2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of 1,3-dichloropropene and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for 1,3-dichloropropene based on toxicological studies and epidemiological investigations.

1,3-Dichloropropene is widely used as a preplanting soil fumigant for the control of nematodes, and it has been available for agricultural use in many formulations. Formulations, instead of pure 1,3-dichloropropene, were used in most of the studies discussed here. The trade names and components of these formulation are listed below:

Formulation	Composition
Telone®	40.2% cis, 38.3% trans (not otherwise specified)
Telone C-17®	40%-41% cis, 38%-39% trans 19%-21% chloropicrin
Telone II®a	48-53% cis, 42-45% trans 1% epichlorohydrin (not otherwise specified)
Telone II®b	48%-53% cis, 42%-45% trans 2% epoxidized soybean oil
DD®	25%-28% cis, 25%-27% trans 25%-29% 1,2-dichloropropane
DD-92®	92% cis/trans (not otherwise specified)
M-3993	48%-53% cis, 42%-45% trans 1% epichlorohydrin (not otherwise specified)

In some studies, the investigation of the toxicity of 1,3-dichloropropene may have been confounded by other components in a formulation (e.g., chloropicrin and epichlorohydrin). This possibility is discussed in the appropriate sections of the text. Separate tables and figures for each formulation of 1,3-dichloropropene are not presented. Instead, the formulation used in each study is identified in the appropriate

table. Further information on the formulations of 1,3-dichloropropene can be found in Chapter 4.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods- -acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing noobserved- adverse-effect levels (NOAELS) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability from laboratory animal data to humans.

Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these

kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

2.2.1.1 Death

No studies were located regarding death in humans after inhalation exposure to 1,3-dichloropropene.

LC_{50} values for inhalation exposure to 1,3-dichloropropene have been determined in rats (Streeter and Lomax 1988; Streeter et al. 1987). The LC_{50} for female rats exposed to Telone II®a for 4 hours was 904 ppm (95% confidence interval= 846-990 ppm) (Streeter et al. 1987). The LC_{50} for male rats could not be determined in this study but fell in the range 855-1035 ppm 1,3-dichloropropene. Telone C-17® appears to be more toxic than Telone II's; the LC_{50} for rats after a l-hour exposure to Telone C-17® was 253 ppm (no range reported) (Streeter and Lomax 1988). Telone C-17® contains a relatively high proportion of chloropicrin, which may account for the enhanced toxicity. Six of 10 rats died after a 4-hour exposure to 676 ppm Telone II®a. In the same study, no rats died after a 4-hour exposure to 595 ppm or less of Telone II®a (Cracknell et al. 1987).

Rabbits exposed to 300 ppm during gestation days 6-18 developed ataxia and died (Kloes et al. 1983). The cause of death was not determined, although lung congestion and edema were noted on necropsy.

Intermediate- or chronic-duration exposures of mice, rats, guinea pigs, rabbits, and dogs to Telone II®a or Telone 11% (l-150 ppm for 4 weeks to 2 years) had no effect on survival rates compared to control groups that were untreated or exposed to filtered room air (Coate 1979a, 1979b; Linnett et al. 1988; Lomax et al. 1989; Stott et al. 1988; Torkelson and Oyen 1977).

The LC_{50} values, the highest NOAEL values, and all reliable LOAELs for death in each species and duration category are recorded in Table 2-l and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

The systemic effects observed in humans and animals after inhalation exposure to 1,3-dichloropropene are discussed below. The highest NOAEL values and all reliable LOAEL values for each systemic effect for each species and duration category are recorded in Table 2-l and plotted in Figure 2-1.

Respiratory Effects. Humans exposed to 1,3-dichloropropene (not otherwise specified) after a tank truck spill complained of mucous membrane

TABLE 2-1. Levels of Significant Exposure to 1,3-Dichloropropene - Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference	Formulation
ACUTE EXPOSURE								
Death								
1	Rat	1 d 1 hr/d				253 (LC_{50})	Streeter and Lomax 1988	T C-17
2	Rat	1 d 4 hr/d				904 (LC_{50} females)	Streeter et al. 1987	T IIa
3	Rat	1 d 4 hr/d		595		676 (6/10 died)	Cracknell et al. 1987	T IIa
4	Rabbit	13 d Gd 6-18 6 hr/d		150		300 (6/7 died)	Kloes et al. 1983	T IIa
Systemic								
5	Rat	1 d 4 hr/d	Resp Other	582 595	595 (swollen lungs) 676 (adrenal congestion)	676 (lung congestion)	Cracknell et al. 1987	T IIa
6	Rat	1 d 1 hr/d	Resp Derm/oc		206 (atelectasis) 206 (eye irritation)		Streeter and Lomax 1988	T C-17
7	Rat	1 d 4 hr/d	Resp Derm/oc		775 (eye irritation)	1,035 (lung hemorrhage)	Streeter et al. 1987	T IIa
8	Rat	1 d 1 hr/d	Derm/oc			1,146 (eye irritation)	Yakel and Kociba 1977	T IIa
Neurological								
9	Rabbit	13 d 6 hr/d		150	300 (ataxia)		Kloes et al. 1983	T IIa
Developmental								
10	Rat	10 d Gd 6-15 6 hr/d		150		300 (decreased litter size)	Kloes et al. 1983	T IIa

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference	Formulation
11	Rabbit	13 d Gd 6-18 6 hr/d		150			Kloes et al. 1983	T IIa
INTERMEDIATE EXPOSURE								
Death								
12	Rat	13 wk 5 d/wk 6 hr/d		150			Stott et al. 1988	T IIa
13	Rabbit	6 mo 5 d/wk 0.5-4 hr/d		3			Torkelson and Oyen 1977	T IIa
14	Gn pig	6 mo 5 d/wk 0.5-4 hr/d		3			Torkelson and Oyen 1977	T IIa
15	Mouse	13 wk 5 d/wk 6 hr/d		150			Stott et al. 1988	T IIa
16	Dog	6 mo 5 d/wk 0.5-4 hr/d		3			Torkelson and Oyen 1977	T IIa
Systemic								
17	Rat	13 wk 5 d/wk 6 hr/d	Resp Cardio Hepatic Renal	10[b] 90 90 90	30 (nasal epithelial changes)		Coate 1979a	T IIa
18	Rat	10 wk 5 d/wk 6 hr/d	Hemato Hepatic Renal	90 90 90			Linnett et al. 1988	DD[•]

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference	Formulation
19	Rat	180 d 5-7 d/wk 6 hr/d	Resp Gastro Hepatic Renal	30 90 90 90	90 (nasal lesions)		Breslin et al. 1989	T IIb
20	Rat	13 wk 5 d/wk 6 hr/d	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Derm/oc	30 150 150 150 150 150 150 150	90 (nasal hyperplasia)		Stott et al. 1988	T IIa
21	Rat	6 mo 5 d/wk 7 hr/d	Resp Cardio Hemato Hepatic	3 3 3 3			Torkelson and Oyen 1977	T IIa
22	Rabbit	6 mo 5 d/wk 0.5-4 hr/d	Resp Cardio Hemato Hepatic Renal	3 3 3 3 3			Torkelson and Oyen 1977	T IIa
23	Gn pig	6 mo 5 d/wk 0.5-4 hr/d	Resp Cardio Hemato Hepatic Renal	3 3 3 3 3			Torkelson and Oyen 1977	T IIa

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference	Formulation
24	Mouse	13 wk 5 d/wk 6 hr/d	Resp	30	90 (nasal hyperplasia)		Stott et al. 1988	T IIa
			Cardio	150				
			Gastro	150				
			Hemato	150				
			Musc/skel	150				
			Hepatic	150				
			Renal	30	90 (bladder hyperplasia)			
25	Mouse	6-12 mo 5 d/wk 6 hr/d	Resp	5	20 (hyperplasia)		Lomax et al. 1989	T IIb
			Cardio	60				
			Gastro	60				
			Hemato	60				
			Musc/skel	60				
			Hepatic	60				
			Renal	20	60 (bladder hyperplasia)			
			Derm/oc	60				
26	Mouse	13 wk 5 d/wk 6 hr/d	Resp		90 (nasal epithelial changes)		Coate 1979a	T IIa
			Cardio	90				
			Hepatic	90				
			Renal	90				
27	Dog	6 mo 5 d/wk 0.5-4 hr/d	Resp	3			Torkelson and Oyen 1977	T IIa
			Cardio	3				
			Gastro	3				
			Hemato	3				
			Musc/skel	3				
			Renal	3				
Immunological								
28	Rat	6-12 mo 5 d/wk 6 hr/d		60			Lomax et al. 1989	T IIb

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference	Formulation
29	Rat	13 wk 5 d/wk 6 hr/d		150			Stott et al. 1988	T IIa
30	Rat	6-12 wk 5 d/wk 6 hr/d		50			Parker et al. 1982	DD[●]
31	Mouse	13 wk 5 d/wk 6 hr/d		150			Stott et al. 1988	T IIa
32	Mouse	6-12 mo 5 d/wk 6 hr/d		60			Lomax et al. 1989	T IIb
33	Mouse	6-12 wk 5 d/wk 6 hr/d		50			Parker et al. 1982	DD[●]
Neurological								
34	Rat	6-12 mo 5 d/wk 6 hr/d		60			Lomax et al. 1989	T IIb
35	Rat	13 wk 5 d/wk 6 hr/d		150			Stott et al. 1988	T IIa
36	Rat	6-12 wk 5 d/wk 6 hr/d		50			Parker et al. 1982	DD[●]
37	Rabbit	6 mo 5 d/wk 0.5-4 hr/d		3			Torkelson and Oyen 1977	T IIa

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference	Formulation
38	Gn pig	6 mo 5 d/wk 0.5-4 hr/d		3			Torkelson and Oyen 1977	T IIa
39	Mouse	6-12 wk 5 d/wk 6 hr/d		50			Parker et al. 1982	DD[•]
40	Mouse	6-12 mo 5 d/wk 6 hr/d		60			Lomax et al. 1989	T IIb
41	Mouse	13 wk 5 d/wk 6 hr/d		90			Coate 1979a	T IIa
42	Mouse	13 wk 5 d/wk 6 hr/d		150			Stott et al. 1988	T IIa
43	Dog	6 mo 5 d/wk 0.5-4 hr/d		3			Torkelson and Oyen 1977	T IIa
Developmental								
44	Rat	180 d 5-7 d/wk 6 hr/d		90			Breslin et al. 1989	T IIb
Reproductive								
45	Rat	6-12 mo 5 d/wk 6 hr/d		60			Lomax et al. 1989	T IIb
46	Rat	180 d 5-7 d/wk 6 hr/d		90			Breslin et al. 1989	T IIb

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference	Formulation
47	Rat	6-12 wk 5 d/wk 6 hr/d		50			Parker et al. 1982	DD[●]
48	Rat	10 wk 5 d/wk 6 hr/d		90			Linnett et al. 1988	DD[●]
49	Rat	13 wk 5 d/wk 6 hr/d		150			Stott et al. 1988	T IIa
50	Mouse	6-12 mo 5 d/wk 6 hr/d		60			Lomax et al. 1989	T IIb
51	Mouse	13 wk 5 d/wk 6 hr/d		150			Stott et al. 1988	T IIa
52	Mouse	6-12 wk 5 d/wk 6 hr/d		50			Parker et al. 1982	DD[●]
CHRONIC EXPOSURE								
Death								
53	Rat	2 yr 5 d/wk 6 hr/d		60			Lomax et al. 1989	T IIb
54	Mouse	2 yr 5 d/wk 6 hr/d		60			Lomax et al. 1989	T IIb

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference	Formulation
Systemic								
55	Rat	2 yr 5 d/wk 6 hr/d	Resp	20	60 (epithelial degeneration)		Lomax et al. 1989	T IIb
			Cardio	60				
			Gastro	60				
			Hemato	60				
			Musc/skel	60				
			Hepatic	60				
			Renal	60				
			Derm/oc	60				
56	Mouse	2 yr 5 d/wk 6 hr/d	Resp	5[c]	20 (hyperplasia)		Lomax et al. 1989	T IIb
			Cardio	60				
			Gastro	20	60 (hyperplasia)			
			Hemato	60				
			Musc/skel	60				
			Hepatic	60				
			Renal	60				
			Derm/oc	60				
Immunological								
57	Rat	2 yr 5 d/wk 6 hr/d		60			Lomax et al. 1989	T IIb
Neurological								
58	Rat	2 yr 5 d/wk 6 hr/d		60			Lomax et al. 1989	T IIb
59	Mouse	2 yr 5 d/wk 6 hr/d		60			Lomax et al. 1989	T IIb

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference	Formulation
Reproductive								
60	Rat	2 yr 5 d/wk 6 hr/d		60			Lomax et al. 1989	T IIb
61	Mouse	2 yr 5 d/wk 6 hr/d		60			Lomax et al. 1989	T IIb

[a]The number corresponds to the entries in Figure 2-1.
[b]Used to derive an intermediate inhalation minimal risk level (MRL) of 0.003 ppm; concentration adjusted for intermittent exposure, converted to a human equivalent concentration, and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability).
[c]Used to derive a chronic inhalation MRL of 0.002 ppm; dose adjusted for intermittent exposure, converted to a human equivalent concentration, and divided by an uncertainty factor or 100 (10 for extrapolation from animals to humans, and 10 for human variability).

Cardio = cardiovascular; d = day(s); DD® = (25% cis-1,3-dichloropropene, 27% trans-1,3-dichloropropene, 29% 1,2-dichloropropane); Derm/oc = dermal/ocular; Gastro = gastrointestinal; Gd = gestation day; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; T C-17 = Telone C-17® (40% cis-1,3-dichloropropene, 39% trans-1,3-dichloropropene, 21% chloropicrin); T IIa = Telone II® (53% cis-1,3-dichloropropene, 45% trans-1,3-dichloropropene, 1% epichlorohydrin); T IIb = Telone II® (50% cis-1,3-dichloropropene, 43% trans-1,3-dichloropropene, 2% epoxidized soybean oil); wk = week(s); yr = year(s)

FIGURE 2-1. Levels of Significant Exposure to 1,3-Dichloropropene - Inhalation

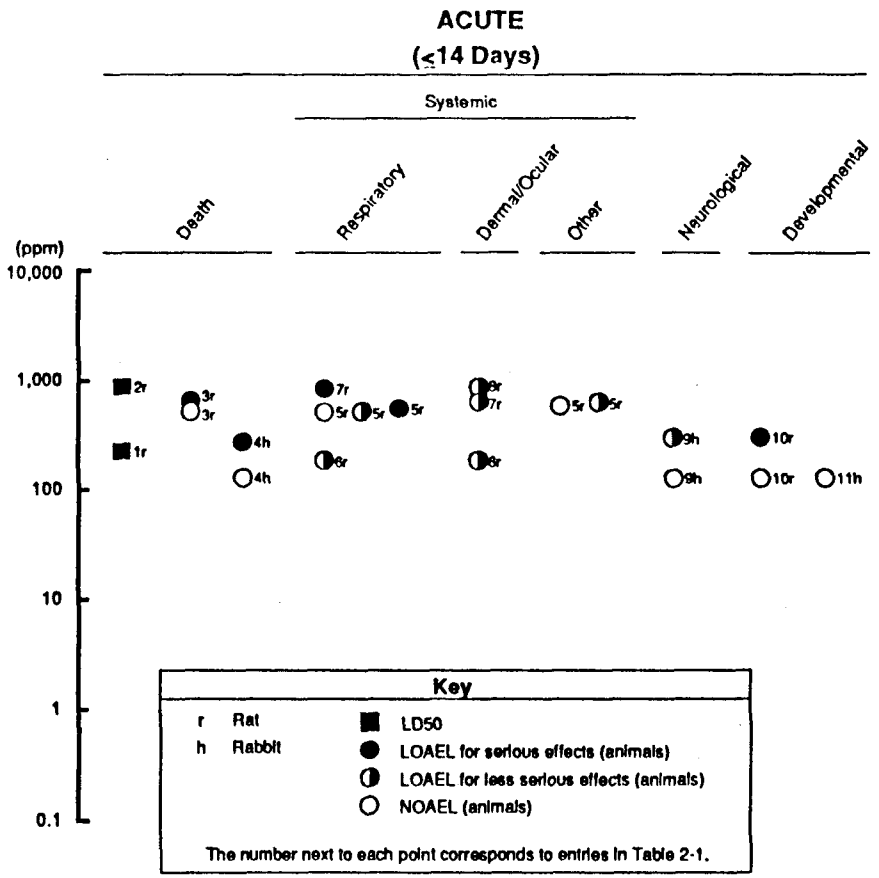


FIGURE 2-1 (Continued)

INTERMEDIATE
(15-364 Days)

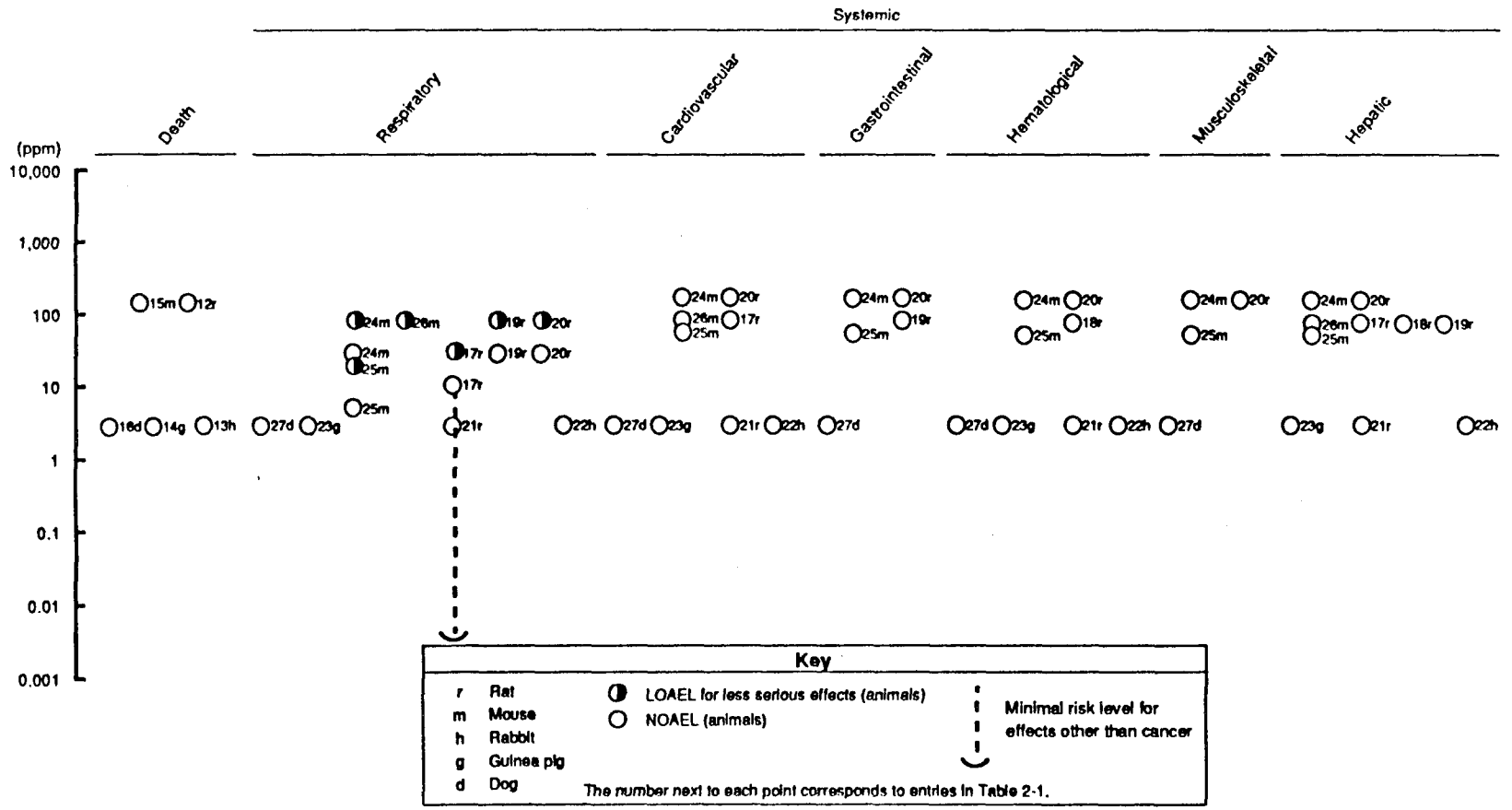


FIGURE 2-1 (Continued)

INTERMEDIATE (Continued)
(15-364 Days)

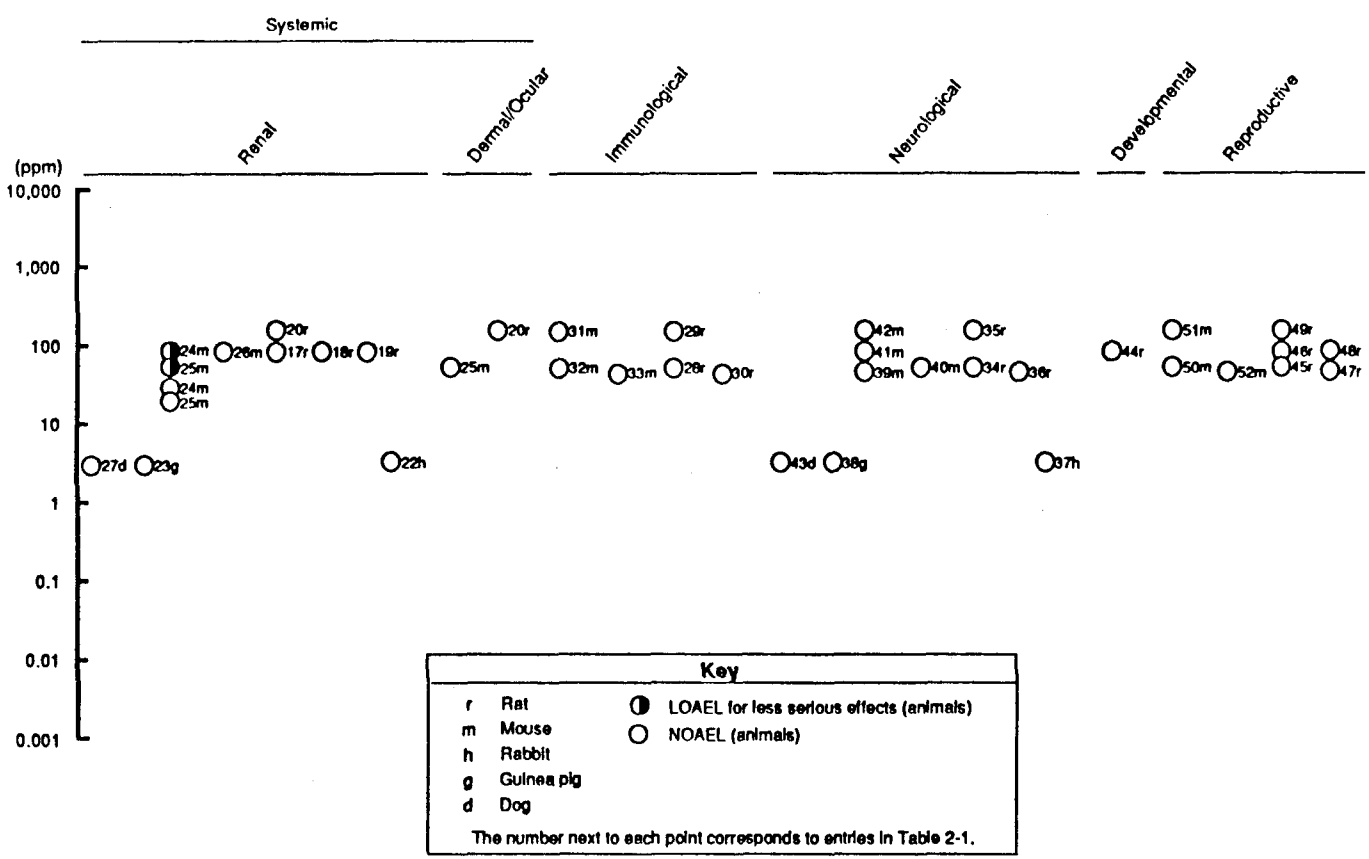
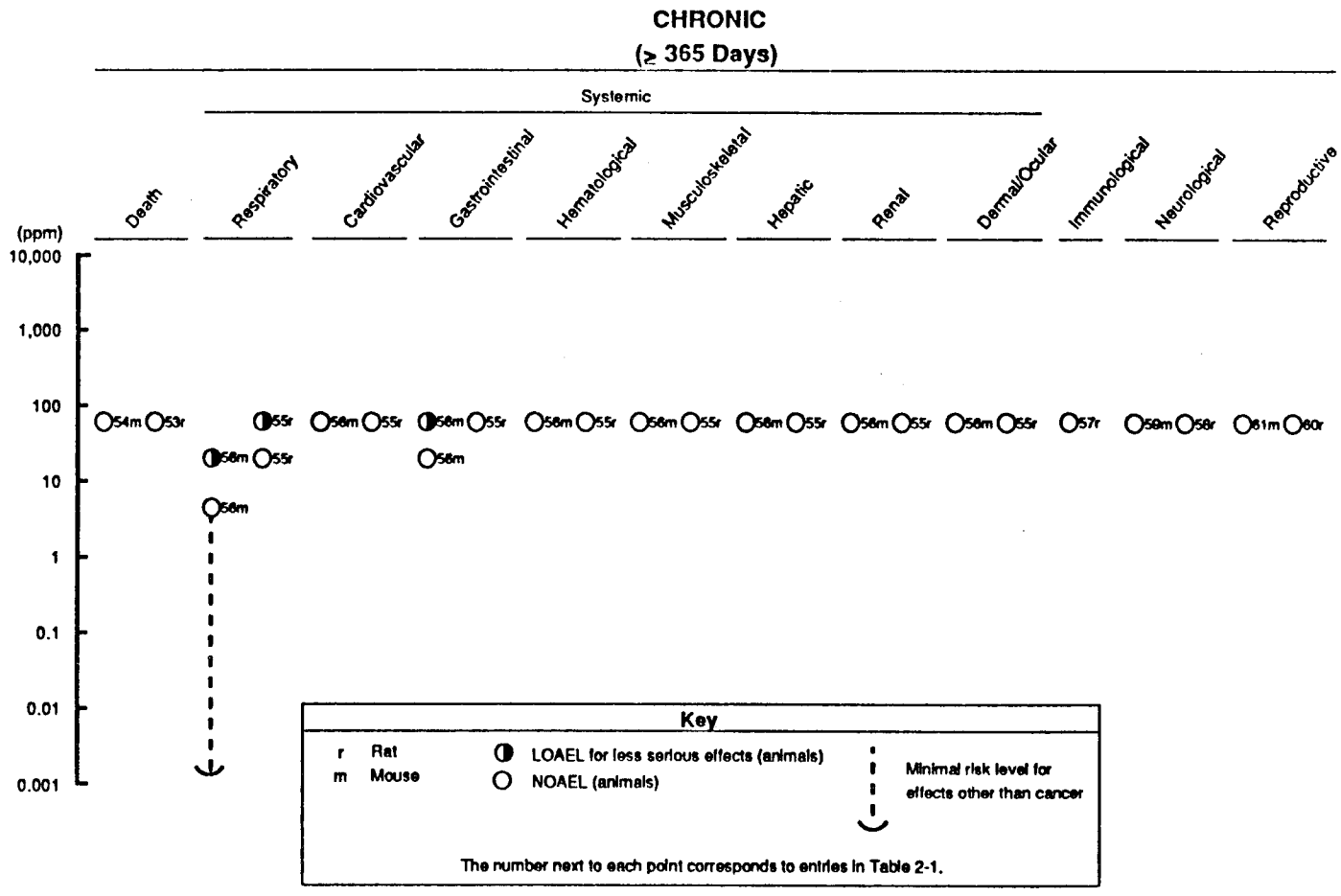


FIGURE 2-1 (Continued)



irritation, chest pain, cough, and breathing difficulties (Flessel et al. 1978; Markovitz and Crosby 1984).

Acute-duration exposures of rats to various formulations of 1,3-dichloropropene caused respiratory effects. Gross pathological examination revealed atelectasis, emphysema, and/or edema in rats exposed to 206 ppm of Telone C-17® for 1 hour. Atelectasis was still present in animals surviving the 2-week observation period (Streeter and Lomax 1988). As noted for death in Section 2.2.1.1, Telone C-17® also appears to be more toxic than Telone II®a after acute-duration exposure. The presence of chloropicrin may enhance the toxicity of Telone C-17®. No respiratory effects were noted in rats after a 4-hour exposure to 582 ppm of Telone II®a, although swollen lungs were observed in rats after a 4-hour exposure to 595 ppm. This indicated a steep concentration-response curve (Cracknell et al. 1987). In the same study, rats exposed to 676 ppm had lung congestion, tracheal congestion, and fluid in the thoracic cavity (Cracknell et al. 1987). Multifocal lung hemorrhage was observed in rats exposed for 4 hours to 1,035 ppm of Telone II®a (Streeter et al. 1987).

Intermediate-duration exposure studies indicate that effects on the upper respiratory tract appear to be concentration- and duration-related. Rats and mice had no respiratory lesions attributable to Telone II®a after exposure to 30 ppm or less for 4 weeks (Coate 1979b). Similarly, no respiratory lesions attributable to DD® were observed after gross and microscopic evaluation of rats exposed to 50 ppm or less for 6-12 weeks (Parker et al. 1982). No respiratory effects were observed in rats exposed to 10 ppm Telone II®a for 13 weeks (Coate 1979a). In contrast, rats exposed to 30 ppm Telone II®a or more for 13 weeks developed epithelial changes in the nasal turbinates that included loss of cytoplasm, nuclei disorganization, and occasional necrotic cells (Coate 1979a). Based on the NOAEL for respiratory effects from this study (Coate 1979a), an intermediate inhalation MRL of 0.003 ppm was calculated as described in the footnote to Table 2-1. The epithelial lesions were more severe in rats exposed to 90 ppm or more of Telone II®a for 13 weeks or more and included hyperplasia and focal necrosis (Breslin et al. 1989; Coate et al. 1979a; Stott et al. 1988). No significant respiratory effects were observed in rats exposed to 60 ppm Telone IIb, the highest concentration tested, for 6 or 12 months (Lomax et al. 1989). Mice also developed hyperplastic and/or degenerative lesions of the nasal epithelium after exposure to 90 ppm Telone II®a for 13 weeks (Stott et al. 1988) or to 20 or 60 ppm Telone 11®b for 6-12 months. No respiratory effects were noted on gross and histopathological examinations after an intermediate inhalation exposure of rats, guinea pigs, rabbits, or dogs to 3 ppm Telone II®a for 6 months (Torkelson and Oyen 1977). Higher concentrations were not tested.

Although exposure to 60 ppm of Telone 11®b for 6-12 months did not result in respiratory effects in rats, exposure to the same concentration for 2 years caused olfactory epithelium degeneration (Lomax et al. 1989). A statistically

significant increase in bronchioalveolar adenomas, benign lung tumors, was also noted in males exposed to 60 ppm but not in females. In mice exposed to 20 or 60 ppm Telone II®b, the epithelial hypertrophy/hyperplasia did not progress in severity or extent from 6 to 24 months. Degeneration of the olfactory epithelium, however, was noted in 48 of 50 male mice and 45 of 50 female mice exposed to 60 ppm, and in 1 of 50 males and 1 of 50 females exposed at 20 ppm (Lomax et al. 1989). Based on the NOAEL for respiratory effects in mice in this study, a chronic inhalation MRL of 0.002 ppm was calculated as described in the footnote in Table 2-1.

These data indicate that acute exposure to 1,3-'dichloropropene has effects on the lungs of rats, while intermediate or chronic inhalation exposure to 1,3-dichloropropene produces hyperplastic lesions of the upper respiratory tract in rats and mice and degeneration of the olfactory epithelium in mice.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after inhalation exposure to 1,3-dichloropropene.

No lesions attributable to Telone II®a were found upon histological evaluation of the heart and aorta from rats and mice exposed to 150 ppm or less for up to 13 weeks (Coate 1979a, 1979b; Stott et al. 1988), rats and mice exposed to 60 ppm Telone 11®b for 6, 12, or 24 months (Lomax et al. 1989), or rats exposed to 50 ppm DD® for 6-12 weeks (Parker et al. 1982).

Although other indices of cardiovascular toxicity were not examined, 1,3-dichloropropene does not appear to have cardiovascular effects.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to 1,3-dichloropropene.

No gastrointestinal effects were noted after gross and histologic examinations of the stomachs and intestines of rats exposed to 50 ppm or less of DD® for 6-12 weeks (Parker et al. 1982), rats or mice exposed to 150 ppm or less of Telone II®a for 13 weeks (Stott et al. 1988), or rats or mice exposed to 60 ppm of Telone II®b for 6 or 12 months (Lomax et al. 1989). Similarly, no gastrointestinal lesions attributable to 1,3-dichloropropene were observed in rats exposed to 60 ppm of Telone 11®b for 2 years (Lomax et al. 1989). In contrast, 8 of 50 male mice exposed to 60 ppm Telone II® for 2 years had hyperplasia and hyperkeratosis of the forestomach. The NOAEL for this effect was 20 ppm in the male mice. Female mice did not develop hyperplasia or hyperkeratosis of the forestomach (Lomax et al. 1989).

Hematological Effects. No studies were located regarding hematological effects in humans after inhalation exposure to 1,3-dichloropropene.

Hematological parameters have been examined in many studies of intermediate or chronic duration in which several species were exposed by inhalation to formulations of 1,3-dichloropropene. No exposure-related hematological effects were observed in rats, guinea pigs, rabbits, or dogs exposed to 3 ppm Telone II®a for 6 months (Torkelson and Oyen 1977), in rats and mice exposed to 150 ppm Telone 1I®a for 13 weeks (Stott et al. 1988), to 60 ppm Telone II®b for 6-24 months (Lomax et al. 1989), or in male or female rats exposed to DD® at concentrations up to 90 ppm for up to 10 weeks (Linnett et al. 1988; Parker et al. 1982).

Histological examination of bone marrow also did not reveal any adverse effects in either intermediate or chronic duration exposure studies (Lomax et al. 1989; Stott et al. 1988).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to 1,3-dichloropropene.

Gross and histopathological examination of bone and skeletal muscle did not reveal any differences between exposed and control groups of rats and mice exposed to up to 50 ppm DD® for 6-12 weeks (Parker et al. 1982), 150 ppm Telone II®a for 13 weeks (Stott et al. 1988), or 60 ppm Telone II®b for 6-24 months (Lomax et al. 1989).

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation exposure to 1,3-dichloropropene.

Gross and histopathological examination of livers did not reveal any differences between exposed and control groups of rats and mice after inhalation exposure to up to 150 ppm of Telone II®a for 13 weeks or less (Coate et al. 1979b; Stott et al. 1988), up to 50 ppm DD® for 6-12 weeks (Parker et al. 1982), or up to 60 ppm Telone II®b for 24 months or less (Lomax et al. 1989).

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to 1,3-dichloropropene.

Male and female rats exposed to 3 ppm Telone II®a for 6 months developed reversible cloudy swelling of the renal tubular epithelium (Torkelson and Oyen 1977). No adverse renal effects were observed in rats allowed to recover for 3 months following the last exposure. The cloudy swelling observed in these rats was not confirmed in more recent studies, even at longer durations and/or higher concentrations. Exposure to 1 ppm in this study had no renal effects in the rats. Guinea pigs, rabbits, and dogs exposed to 3 ppm suffered no renal effects under the same exposure protocol (Torkelson and Oyen 1977).

Gross and histological examination of the kidneys from rats and mice exposed to up to 150 ppm Telone II®a for 4-13 weeks (Coate et al. 1979b; Stott et al. 1988), to 50 ppm DD® for 6-12 weeks (Parker et al. 1982), or to 60 ppm Telone II®b for 6-24 months (Lomax et al. 1989) revealed no differences between exposed and control groups. Urinalysis also revealed no differences between exposed and control groups of rats and mice (Lomax et al. 1989; Parker et al. 1982; Stott et al. 1988).

Moderate hyperplasia of the transitional epithelium of the urinary bladder was found in female mice exposed to 90 or 150 ppm Telone 1I®a for 13 weeks (Stott et al. 1988). Mice exposed to 30 ppm did not show hyperplasia of the urinary bladder. Similarly, mice exposed to up to 60 ppm Telone II®a for 6-24 months did not show hyperplasia of the urinary bladder (Lomax et al. 1989).

Female mice administered Telone II®a in a 2-year gavage study also showed a dose-related increase in urinary bladder hyperplasia (Section 2.2.2.2) (NTP 1985).

Dermal/Ocular Effects. No studies were located regarding dermal or ocular effects in humans after inhalation exposure to 1,3-dichloropropene.

Gross and histological examination of the eyes and skin of rats and mice exposed to up to 150 ppm Telone II®a for 13 weeks (Stott et al. 1988) to 60 ppm for 6-24 months (Lomax et al. 1989) revealed no differences between exposed and control groups.

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans after inhalation exposure to 1,3-dichloropropene.

Gross and histological examination of the thymus and lymph nodes of rats and mice exposed to 150 ppm or less of Telone II®a for 13 weeks (Stott et al. 1982), to 60 ppm Telone II®b for 6-24 months (Lomax et al. 1989), or to.50 ppm of DD® for 6-12 weeks (Parker et al. 1982) revealed no lesions attributable to 1,3-dichloropropene exposure. However, more sensitive tests for immune system function were not used.

The highest NOAEL values for each species and duration category are recorded in Table 2-l and plotted in Figure 2-1.

2.2.1.4 Neurological Effects

No neurological effects were.observed in humans occupationally exposed to 1,3-dichloropropene at levels high enough to require medical attention (Markovitz and Crosby 1984).

Ataxia of the hindlimbs and loss of the righting reflex was observed in pregnant rabbits exposed to 300 ppm of Telone II®a during gestation days 6-18. No neurological signs of toxicity were observed in rabbits exposed to 50 or 150 ppm nor in rats exposed to 300 ppm (Kloes et al. 1983).

No clinical signs of neurotoxicity were observed in rats, guinea pigs, rabbits, or dogs after inhalation exposure to 3 ppm Telone II®a for 6 months (Torkelson and Oyen 1977), in rats or mice exposed to up to 150 ppm Telone II®a for 13 weeks (Coate 1979a; Stott et al. 1988), or to 60 ppm Telone II®b for 6-24 months (Lomax et al. 1989). The absence of clinical signs is supported by histological examinations of brain and spinal cords in rats and mice that revealed no lesions attributable to 1,3-dichloropropene exposure (Coate 1979a; Lomax et al. 1989; Stott et al. 1988). More sensitive tests for neurological effects, however, were not included in these studies.

The acute LOAEL value in rabbits and the highest NOAEL values for neurological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to 1,3-dichloropropene.

No developmental effects were found in groups of rats exposed to 50 or 150 ppm Telone II®a during gestation days 6-15 (Kloes et al. 1983). In contrast, rats exposed to 300 ppm Telone II®a during gestation days 6-15 had fewer fetuses per litter, an increase in the incidence of litters totally resorbed, and an increase in the number of litters with resorptions. Rats exposed to 300 ppm Telone 1I®a had urine and fecal staining, nasal exudate, a red crusty material around the eyes, and significantly decreased food and water consumption and body weight. These observations indicate serious maternal toxicity in rats exposed to 300 ppm, which could account for the decreased litter size, increased resorptions, and increased number of litters with resorptions. Rabbits were evaluated for developmental effects after exposure to up to 300 ppm Telone II®a during gestation days 6-18 (Kloes et al. 1983). No developmental effects attributable to 1,3-dichloropropene exposure were observed in the 50 and 150 ppm groups. In contrast, marked maternal toxicity in the 300 ppm group precluded evaluation of developmental effects; signs of maternal toxicity included ataxia, loss of the righting reflex, significantly decreased body weight, and the death of six of seven rabbits.

No developmental effects were observed in the progeny of groups of male and female rats exposed to 90 ppm or less Telone II®b for two generations (Breslin et al. 1989), or in pregnant rats and rabbits exposed to 120 ppm or less Telone II®a during gestation days 6-15 (Hanley et al. 1987). The parameters monitored included pup survival, pup body weight, pup crown-rump length, and gross pathology. Delayed ossification was noted in 14 rat pups of

21 litters exposed in utero to 120 ppm, but this may have been due to the decreased food and water consumption and body weight of the dams (Hanley et al. 1987).

The LOAEL in rabbits and the highest NOAEL values for developmental effects are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to 1,3-dichloropropene.

No adverse reproductive effects and no histological changes in reproductive organs were observed in parental groups or progeny of male and female rats exposed to up to 90 ppm Telone II®b for two generations (Breslin et al. 1989). Male and female rats evaluated for libido, fertility, estrus cycling (females), and histological changes of reproductive organs showed no adverse effects after exposure to 90 ppm DD® for 10 weeks (Linnett et al. 1988).

Gross and histological examination of reproductive organs and tissues of rats and mice exposed to 150 ppm of Telone II®a for 13 weeks (Stott et al. 1988), 60 ppm Telone II®a for 6-24 months (Lomax et al. 1989), or 50 ppm of DDe for 6-12 weeks (Parker et al. 1982) revealed no lesions attributable to 1,3-dichloropropene. More sensitive tests for reproductive effects, however, were not included in these studies.

The highest NOAEL values for intermediate-duration reproductive effects in each species are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxicity in humans or animals after inhalation exposure to 1,3-dichloropropene.
Other genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located that convincingly link inhalation exposure to 1,3-dichloropropene with the development of cancer in humans. A clinical report describing three cases of neoplasms that developed after exposure to 1,3-dichloropropene, however, suggests that there may be an association (Markovitz and Crosby 1984). Nine firemen were exposed to 1,3-dichloropropene during cleanup of a tank truck spill. Six years later, two of the men developed histiocytic lymphomas that were refractory to treatment. Both men soon died. In addition, a 52-year-old farmer who had been in good health developed pain in the right ear, nasal mucosa, and pharynx after being exposed

to 1,3-dichloropropene (not otherwise specified) from his tractor for 30 days. The hose carrying the 1,3-dichloropropene had a small leak that sprayed the chemical near the right side of the man's face. Over the next year, the man developed leukemia that was refractory to treatment. He died of pneumonia 5 weeks after hospital admission.

In the only study regarding the carcinogenic potential of 1,3-dichloropropene in animals after inhalation exposure, a statistically significant increase in the incidence of bronchioalveolar adenomas was observed in male mice exposed to 60 ppm Telone II®b for 24 months (Lomax et al. 1989). An increased incidence of this benign lung tumor, however, was not observed in female mice nor in male or female rats exposed to Telone II®b under the same protocol.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to 1,3-dichloropropene.

Several studies were located that reported oral LD_{50} values for 1,3-dichloropropene in various formulations. The oral LD_{50} for M-3993 was 713 mg/kg (no range calculable) in male rats and 470 mg/kg (95% confidence limits-337-636 mg/kg) in female rats (Lichy and Olson 1975). In a similar study, the oral LD_{50} for Telone C-17® was 519 mg/kg (95% confidence interval-305-1,009 mg/kg) in male rats and 304 mg/kg (95% confidence interval-147-516 mg/kg) in female rats (Mizell et al. 1988). These data indicate that female rats are more sensitive to 1,3-dichloropropene in its various formulations than male rats. A much lower LD_{50} value of 150 mg/kg (95% confidence interval-130-170 mg/kg) was reported for Telone II®a in WY-strain Sprague-Dawley rats (Jones and Collier 1986a). Similarly, the LD_{50} value determined for the cis-isomer of 1,3-dichloropropene for male and female rats combined was 121 mg/kg (95% confidence interval-107-137 mg/kg); for male rats only, 126 mg/kg (95% confidence interval=108-148 mg/kg); and for female rats only, 117 mg/kg (95% confidence interval=96-142 mg/kg) (Jones 1988a). The variability in LD_{50} values could result from different rat stocks or strains, or, more likely, from differences in the 1,3-dichloropropene formulations used.

No deaths were reported among rats that received gavage doses of Telone® for 13 weeks (Til et al. 1973). No differences were observed in the survival rates of rats that received 0, 25, or 50 mg/kg, or of mice that received 0, 50, or 100 mg/kg Telone II®b by gavage in corn oil for 2 years (NTP 1985).

The LD_{50} values in rats and the highest NOAEL values for death in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

TABLE 2-2. Levels of Significant Exposure to 1,3-Dichloropropene - Oral

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Formulation
ACUTE EXPOSURE									
Death									
1	Rat	(GO)	1 d 1x/d				150 (LD_{50})	Jones and Collier 1986a	T IIa
2	Rat	(GO)	1 d 1x/d		75		121 (LD_{50})	Jones 1988a	cis
3	Rat	(G)	1 d 1x/d				713 (LD_{50} - males) 470 (LD_{50} - females)	Lichy and Olson 1975	M-3993
4	Rat	(GO)	1 d 1x/d				519 (LD_{50} - males) 304 (LD_{50} - females)	Mizzell et al. 1988a	T C-17
Systemic									
5	Rat	(GO)	1 d 1x/d	Gastro		100 (hyperkeratosis)		Mizell et al. 1988a	T C-17
6	Rat	(GO)	1 d 1x/d	Resp Gastro Hepatic			110 (lung hemorrhage) 110 (intestinal hemorrhage) 110 (liver hemorrhage)	Jones 1988a	cis
7	Rat	(GO)	1 d 1x/d	Resp Gastro Hepatic Renal	110 110	75 (lung congestion) 75 (multiple white raised areas in nonglandular regions) 170 (mottled, dark liver) 170 (dark kidneys)	250 (lung hemorrhage) 170 (stomach hemorrhage)	Jones and Collier 1986a	T IIa
Neurological									
8	Rat	(GO)	1 d 1x/d			75 (ataxia)		Jones 1988a	cis

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Formulation
INTERMEDIATE EXPOSURE									
Death									
9	Rat	(GO)	13 wk 6 d/wk 1x/d		30			Til et al. 1973	T
Systemic									
10	Rat	(GO)	9 mo 3 d/wk 1x/d	Gastro Hepatic Renal	50 50 50			NTP 1985	T IIa
11	Rat	(GO)	13 wk 6 d/wk 1x/d	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal	30 30 30 30 30 30 30			Til et al. 1973	T
CHRONIC EXPOSURE									
Death									
12	Rat	(GO)	2 yr 3 d/wk 1x/d		50			NTP 1985	T IIa
13	Mouse	(GO)	2 yr 3 d/wk 1x/d		50		100	NTP 1985	T IIa

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Formulation
Systemic									
14	Rat	(GO)	2 yr 3 d/wk 1x/d	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Derm/oc	50 50 50 50 50 50 50	25 (basal cell hyperplasia)		NTP 1985	T IIa
Systemic									
15	Mouse	(GO)	2 yr 3 d/wk 1x/d	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Derm/oc	100 100 100 100 100 100	50 (hyperplasia)	50 (hydronephrosis)	NTP 1985	T IIa
Immunological									
16	Rat	(GO)	2 yr 3 d/wk 1x/d		50			NTP 1985	T IIa
17	Mouse	(GO)	2 yr 3 d/wk 1x/d		100			NTP 1985	T IIa
Neurological									
18	Rat	(GO)	2 yr 3 d/wk 1x/d		50			NTP 1985	T IIa

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Formulation
19	Mouse	(GO)	2 yr 3 d/wk 1x/d		100			NTP 1985	T IIa
Reproductive									
20	Rat	(GO)	2 yr 3 d/wk 1x/d		50			NTP 1985	T IIa
21	Mouse	(GO)	2 yr 3 d/wk 1x/d		100			NTP 1985	T IIa
Cancer									
22	Rat	(GO)	2 yr 3 d/wk 1x/d				25 (hepatic tumors, forestomach tumors)	NTP 1985	T IIa
23	Mouse	(GO)	2 yr 3 d/wk 1x/d				50 (bladder, forestomach tumors)	NTP 1985	T IIa

[a]The number corresponds to the entries in Figure 2-2.

Cardio = cardiovascular; d = day(s); Derm/oc = dermal/ocular; G = gavage - not specified; Gastro = gastrointestinal; GO = gavage - oil; Hemato = hematological; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M-3993 = Telone II®a; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; T = Telone® (40% cis-1,3-dichloropropene, 38% trans-1,3-dichloropropene); T C-17 = Telone C-17® (40% cis-1,3-dichloropropene, 39% trans-1,3-dichloropropene, 21% chloropicrin); T IIa = Telone II® (53% cis-1,3-dichloropropene, 45% trans-1,3-dichloropropene, 1% epichlorohydrin); wk = week(s); yr = year(s)
x = time(s)

FIGURE 2-2. Levels of Significant Exposure to 1,3-Dichloropropene - Oral

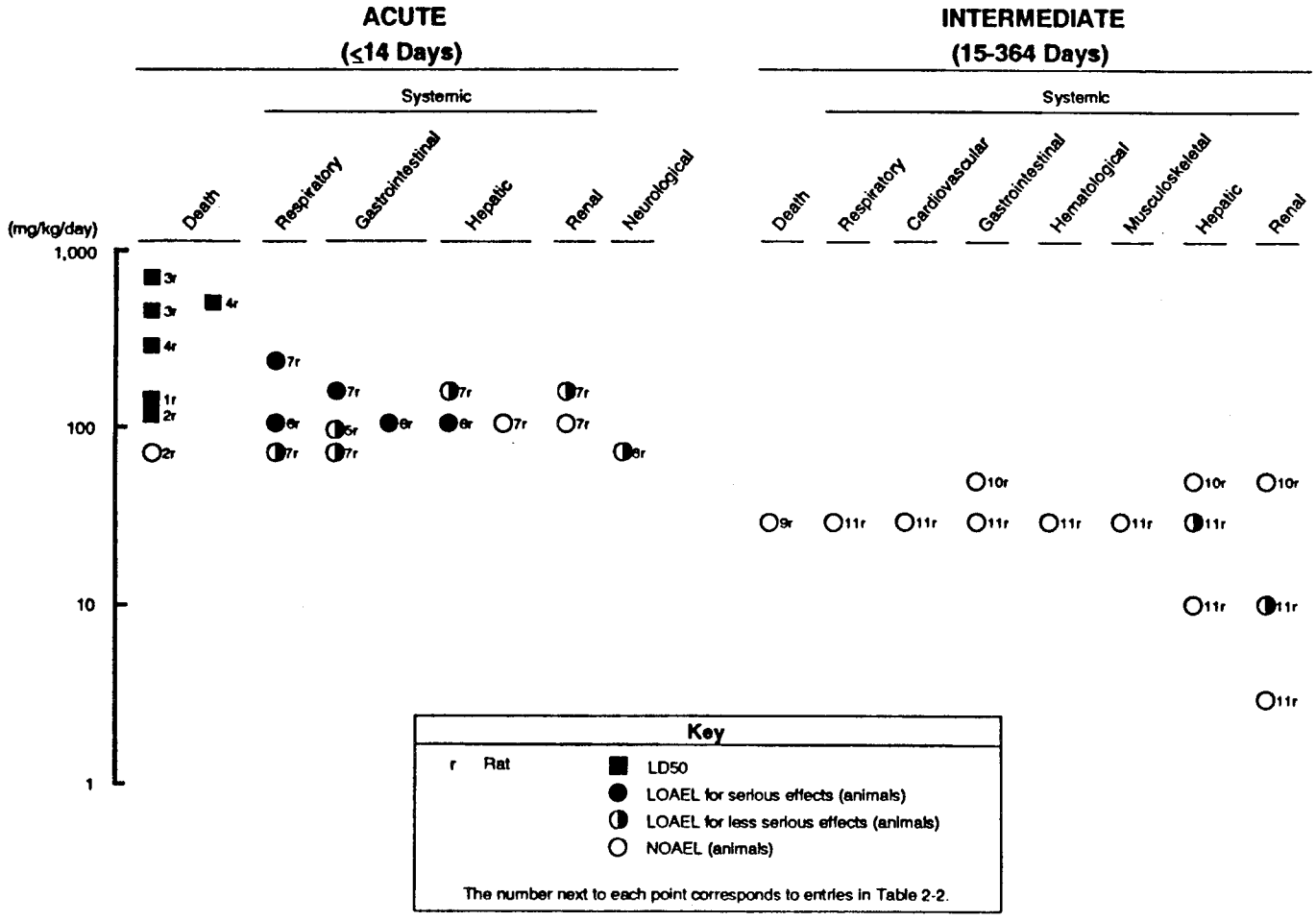
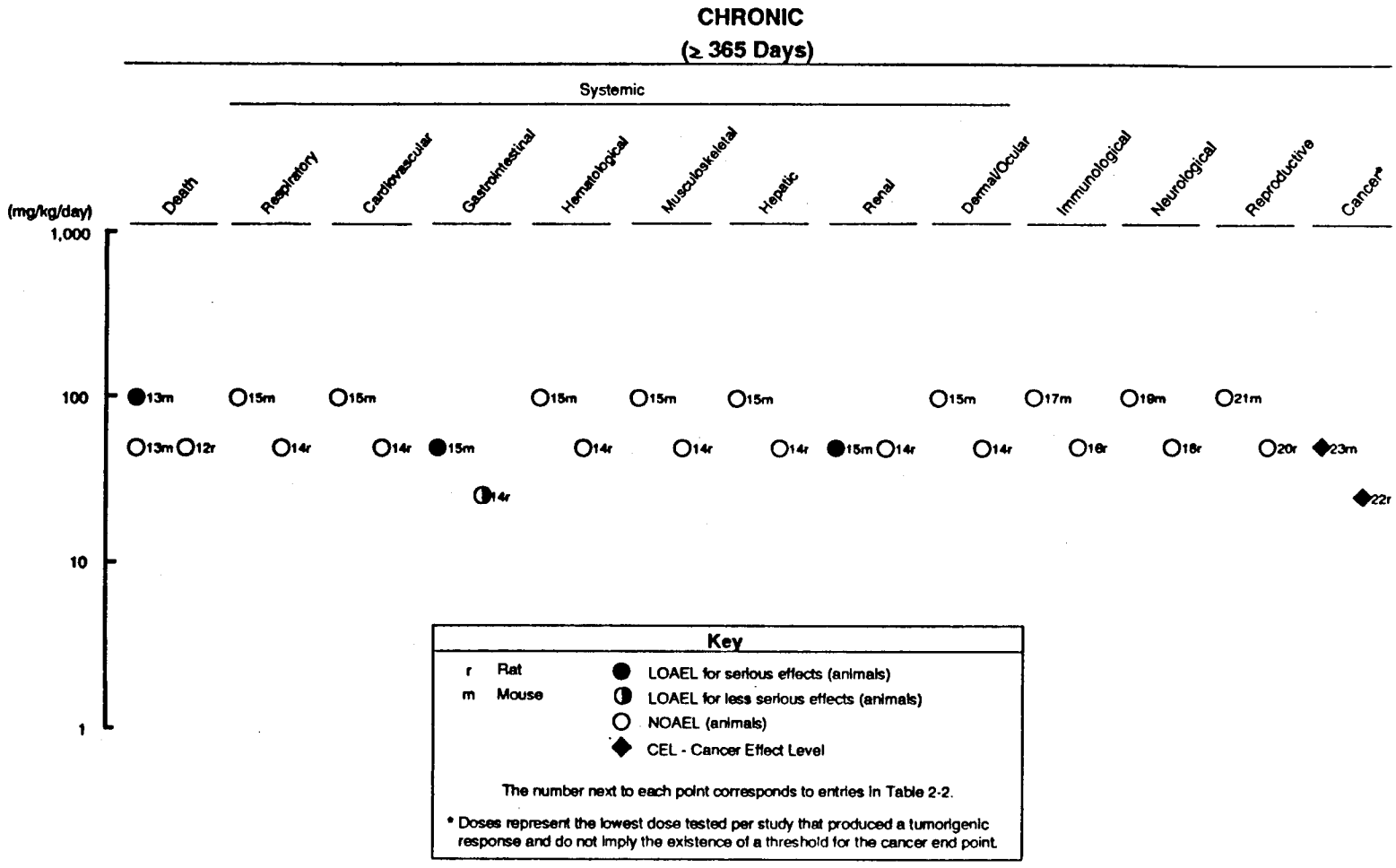


FIGURE 2-2 (Continued)



2.2.2.2 Systemic Effects

The systemic effects observed in animals after oral exposure to 1,3-dichloropropene are discussed below. The highest NOAELs and all reliable LOAELs for each systemic effect for each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to 1,3-dichloropropene.

In a rat LD_{50} study, a single oral administration of Telone II®a caused dose-related respiratory effects including lung congestion and lung hemorrhage (Jones and Collier 1986a). Abnormally red and hemorrhagic lungs were observed in rats that received a single oral dose of cis-1,3-dichloropropene in an LD_{50} study (Jones 1988a).

Gross and microscopic examination of male and female rats that received 30 mg Telone®/kg/day or less for 13 weeks revealed no respiratory effects (Til et al. 1973).

Gross and histological examination revealed no neoplastic or nonneoplastic respiratory lesions in rats and no nonneoplastic respiratory lesions in mice attributable to gavage doses of Telone II®a for 2 years (NTP 1985). In contrast, an increased incidence of bronchioalveolar adenomas was observed in female mice receiving Telone II®a for 2 years (Section 2.2.2.8).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after oral exposure to 1,3-dichloropropene.

Histological evaluation of the hearts of rats that received 30 mg/kg or less of Telone® for 13 weeks revealed no lesions attributable to Telone® (Til et al. 1973).

Gross and histological examination of hearts revealed no cardiovascular lesions in rats that received up to 50 mg/kg or in mice that received up to 100 mg Telone II®a/kg by gavage for 2 years (NTP 1985). Data in male mice were of limited value, because 25 of 50 vehicle controls died of myocarditis after 48-51 weeks.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to 1,3-dichloropropene.

Histological examination of the stomach revealed several raised white patches on the mucosal surface of rats that received a single gavage dose of 75 mg/kg Telone II®a (Jones and Collier 1986a). Rats that received a single oral dose of 110 mg cis-1,3-dichloropropene/kg or more developed ulcerations of the glandular stomach and hemorrhage of the small intestine (Jones 1988a).

Hyperkeratosis of the nor-glandular stomach was found in rats that received a single gavage dose of 100 mg/kg Telone C-17® (Mizell et al. 1988).

Gross and microscopic evaluation of the gastrointestinal tract revealed no lesions attributable to oral administration of 30 mg/kg or less of Telone® to rats for 13 weeks (Til et al. 1973). Similarly, no gastrointestinal lesions were found in rats that received 50 mg/kg or less of Telone II®a for 9 months (NTP 1985).

Chronic oral exposure to 1,3-dichloropropene causes preneoplastic and neoplastic lesions in the gastrointestinal systems of rats and mice. Significant dose-related increases in basal cell or epithelial cell hyperplasia of the forestomach were observed in male and female rats that received 25 mg/kg or more Telone IIea for 2 years (NTP 1985). Additionally, female rats that received 50 mg/kg had hyperkeratosis of the forestomach. Male rats suffered an increase in pancreatic periarteritis at both 25 and 50 mg/kg.

Dose-related increases in epithelial cell hyperplasia of the forestomach were observed in female mice receiving 50 mg/kg or more Telone 1I®a (NTP 1985). Although data in male mice were limited, the incidence of forestomach epithelial cell hyperplasia was similar to that in the females. Neoplastic lesions of the stomach were also observed in rats and mice that received gavage doses of Telone II®a for 2 years (Section 2.2.2.8).

Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to 1,3-dichloropropene.

Evaluation of hematological profiles and clinical chemistry revealed no adverse effects in rats that received 30 mg/kg or less of Telone® (Til et al. 1973).

Extensive clinical chemistry and hematological profiles of male and female rats exposed to up to 50 mg/kg 1,3-dichloropropene for 2 years revealed no signs of adverse effects (NTP 1985). Therefore, 1,3-dichloropropene does not cause adverse hematological effects after oral administration of doses of 50 mg/kg or less for up to 2 years.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to 1,3-dichloropropene.

Gross and histological examination of male rats that received up to 50 mg/kg 1,3-dichloropropene by gavage for 2 years revealed no musculoskeletal effects (NTP 1985). Neither female rats nor male or female mice were examined for musculoskeletal effects.

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to 1,3-dichloropropene.

Rats that received a single gavage dose of 110 mg cis-1,3-dichloropropene/kg or more developed dark and patchy livers and hemorrhage of the liver (Jones 1988a). Similarly, a single gavage dose of 170 mg/kg Telone II®a produced mottled and dark livers in rats (Jones and Collier 1986a).

An increased liver:body weight ratio was observed in rats that received 30 mg/kg, but not 10 mg/kg or less, of Telone® for 13 weeks (Til et al. 1973).

Histological examination revealed no hepatic lesions that were attributable to oral administration of 50 mg/kg Telone II®a to rats for 9-24 months (NTP 1985). Similarly, no hepatic lesions attributable to Telone II®a were found in mice after they received gavage doses for 2 years. In contrast, an increased incidence of hepatic neoplastic nodules was observed in male rats that received Telone II®a for 2 years (Section 2.2.2.8).

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to 1,3-dichloropropene.

A single gavage dose of 170 mg/kg Telone II®a produced dark kidneys in rats (Jones and Collier 1986a). The toxicological significance of this observation was not discussed. The NOAEL for this effect was 110 mg/kg.

An increase in the kidney:body weight ratio was observed in rats that received 10 mg/kg, but not 3 mg/kg, Telone® for 13 weeks (Til et al. 1973). In contrast, no renal lesions were observed after gross and microscopic examination in rats that received 50 mg/kg or less of Telone 1I®a for 9-24 months (NTP 1985).

Female mice developed a dose-related increase in kidney hydronephrosis after oral exposure to 50 or 100 mg/kg Telone 1I®a for 2 years (NTP 1985). A primary target organ of 1,3-dichloropropene in female mice was the urinary bladder, where a dose-related increase in epithelial cell hyperplasia and transitional cell carcinoma (Section 2.2.2.8) was observed. male mice were not adequate, Although data for there was some indication that Telone 1I®a also caused transitional cell carcinomas in the urinary bladder. Similar neoplastic and nonneoplastic lesions were not found in male and female rats exposed to up to 50 mg/kg 1,3-dichloropropene for 2 years (NTP 1985).

Dermal/Ocular Effects. No studies were located regarding dermal/ocular effects in humans after oral exposure to 1,3-dichloropropene.

Gross and histological examination of the eyes and skin in rats and of the skin only in mice that received gavage doses of Telone II®a for 2 years revealed no lesions attributable to Telone II®a (NTP 1985):

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after oral exposure to 1,3-dichloropropene.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to cis-1,3-dichloropropene.

Clinical signs of neurotoxicity were observed at 1 and 4 hours after a single oral dose of 1,3-dichloropropene in rats (Jones 1988a). The observations included hunched posture, pilo-erection, lethargy, ptosis, ataxia, and decreased respiratory rate. More sensitive tests for neurological effects, however, were not used.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals after oral exposure to 1,3-dichloropropene.

2.2.2.6 Reproductive Effects

Histological evaluation of reproductive organs and tissues from rats and mice that received oral doses of Telone 1I®a for 2 years revealed no lesions attributable to the exposure (NTP 1985). More sensitive tests for reproductive effects, however, were not performed in this study.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to 1,3-dichloropropene.

Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans after oral exposure to 1,3-dichloropropene.

Substantial evidence exists for 1,3-dichloropropene-related carcinogenicity in rats and mice after oral exposure. In a 2-year gavage study, rats that received 25 or 50 mg Telone II®a/kg/day developed squamous cell papillomas and carcinomas of the forestomach (NTP 1985). Male rats also developed neoplastic nodules of the liver. Female mice that received 50 or 100 mg/kg/day developed squamous cell papillomas and carcinomas of the forestomach, transitional cell carcinomas of the urinary bladder, and an increased incidence of alveolar/bronchiolar adenomas. The data in male mice

were considered inadequate for assessment of carcinogenicity, because 25 of 50 vehicle controls died of myocarditis during weeks 48-51 of the study; however, there was some indication that the same neoplastic lesions found in increased incidences in female mice also occurred in male mice (NTP 1985). How much the epichlorohydrin component (1%) of Telone 1I®a contributes to the development of papillomas and carcinomas of the forestomach is not known. Although oral administration of epichlorohydrin produced papillomas and carcinomas of the forestomach in male mice (NTP 1989), it is doubtful that Telone II®a contained enough epichlorohydrin for the tumor response to be due solely to epichlorohydrin.

The cancer effect levels (CELs) in rats and mice are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to 1,3-dichloropropene.

The acute dermal LD_{50} for cis-1,3-dichloropropene in male and female rats combined was 794 mg/kg (95% confidence interval-669-942 mg/kg); for males only, 758 mg/kg (95% confidence interval-604-950 mg/kg); and for females only, 841 mg/kg (95% confidence interval-633-1118 mg/kg) (Jones 1988b). The acute dermal LD_{50} for Telone 1I®a in rats was 1,200 mg/kg (95% confidence interval-1,000-1,400 mg/kg) (Jones and Collier 1986b). The acute dermal LD_{50} in rabbits for M-3993 was 713 mg/kg for males and 407 mg/kg for females, for an average of 504 mg/kg (95% confidence limits= 220-1,150 mg/kg) (Lichy and Olson 1975). In a similar study, the dermal LD_{50} for Telone 1I®a in rabbits was 333 mg/kg (95% confidence interval-102-610 mg/kg) (Jeffrey et al. 1987). Six of 10 rabbits died or were submitted to pathology in a moribund condition within 4 days after receiving a dermal application of 500 mg/kg Telone C-17æ (Mizell et al. 1988b).

The LOAEL in rats and the LD_{50} and LOAEL values in rabbits are recorded in Table 2-3.

2.2.3.2 Systemic Effects

The systemic effects observed in animals after dermal exposure to 1,3-dichloropropene are discussed below. The highest NOAEL values and all reliable LOAEL values for each systemic effect for each species and duration category are recorded in Table 2-3.

TABLE 2-3. Levels of Significant Exposure to 1,3-Dichloropropene - Dermal

Species	Exposure frequency/ duration	System	NOAEL	LOAEL (effect) Less Serious	LOAEL (effect) Serious	Reference	Formulation
ACUTE EXPOSURE							
Death							
Rat	1 d 24 hr/d		500 mg/kg		794 mg/kg (LD50)	Jones 1988b	cis
Rat	1 d 24 hr/d		500 mg/kg		1,200 mg/kg (LD_{50})	Jones and Collier 1986b	T IIa
Rabbit	1 d 24 hr/d				500 mg/kg (6/10 died)	Mizell et al. 1988b	T C-17
Rabbit	1 d 24 hr/d				713 mg/kg (LD_{50} - males) 470 mg/kg (LD_{50} - females)	Lichy and Olson 1975	M-3993
Rabbit	1 d 24 hr/d				333 mg/kg (LD_{50})	Jeffrey et al. 1987	T IIa
Systemic							
Rat	1 d 24 hr/d	Resp		500 mg/kg (lung congestion)	800 mg/kg (lung hemorrhage)	Jones and Collier 1986b	T IIa
		Gastro	500 mg/kg		800 mg/kg (stomach hemorrhage)		
		Derm/oc		500 mg/kg (subcutaneous hemorrhage)			
Rat	1 d 24 hr/d	Resp		800 mg/kg (abnormally red lungs)		Jones 1988b	cis
		Gastro			800 mg/kg (stomach hemorrhage, stomach ulcers)		
		Hepatic		800 mg/kg (dark liver)			
		Derm/oc		500 mg/kg (edema, eschar formation, skin hardening)			
Rabbit	1 d 4 hr/d	Derm/oc		0.5 mL (necrosis/ exfoliation)		Mizell 1988a	T C-17

TABLE 2-3 (Continued)

Species	Exposure frequency/ duration	System	NOAEL	LOAEL (effect) Less Serious	LOAEL (effect) Serious	Reference	Formulation
Rabbit	1 d 24 hr/d	Derm/oc		200 mg/kg (erythema, necrosis)		Jeffrey et al. 1987	T IIa
Rabbit	1 d 4 hr/d	Derm/oc		0.5 mL (erythema/edema)		Jeffrey 1987c	T IIa
Rabbit	1 d 1x/d	Derm/oc		0.1 mL (eye irritation)		Lichy and Olson 1975	M-3993
Rabbit	1 d 1x/d	Derm/oc		0.1 mL (eye irritation)		Jeffrey 1987b	T IIa
Rabbit	3 d 1x/d	Derm/oc		0.5 mL (erythema/edema)		Lichy and Olson	M-3993
Rabbit	1 d 24 hr/d	Musc/skel Derm/oc		500 mg/kg (skeletal muscle hemorrhage)	500 mg/kg (necrosis)	Mizell et al. 1988	T C-17
Gn pig	14 wk 1 d/wk 6 hr/d	Derm/oc		0.4 mL of 1% solution (erythema)		Mizell 1988b	T C-17
Gn pig	1 wk 4x/wk	Derm/oc		0.1 mL of 10% solution (erythema)		Carreon and Wall 1983	T IIa
Neurological							
Rat	1 d 24 hr/d			500 mg/kg (lethargy, salivation)	800 mg/kg (decreased respiration, ataxia, ptosis)	Jones 1988b	cis
INTERMEDIATE EXPOSURE							
Systemic							
Gn pig	4 wk 1 d/wk 6 hr/d	Derm/oc		0.4 mL of 0.1% solution (erythema)		Jeffrey 1987a	T IIa

TABLE 2-3 (Continued)

Species	Exposure frequency/ duration	System	NOAEL	LOAEL (effect) Less Serious	LOAEL (effect) Serious	Reference	Formulation
Immunological							
Gn pig	3 wk 3 d/wk 6 hr/d			0.2 mL (contact of a 0.5% solution sensitization)		Jones 1988c	cis

d = day(s); Derm/oc = dermal/ocular; Gastro = gastrointestinal; Gn pig = guinea pig; hr = hour(s); LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M-3993 = Telone IIa; ml = milliliter(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; T C-17 = Telone C-17® (40% cis-1,3-dichloropropene, 39% trans-1,3-dichloropropene, 21% chloropicrin); T IIa = Telone II® (53% cis-1,3-dichloropropene, 45% trans-1,3-dichloropropene, 1% epichlorohydrin); wk = week(s)

No studies were located regarding cardiovascular, hematological, or renal effects in humans or animals after dermal exposure to 1,3-dichloropropene.

Respiratory Effects. No studies were located regarding respiratory effects in humans after dermal exposure to 1,3-dichloropropene. Gross necropsy revealed abnormally red lungs in rats that died after dermal application of 800 mg/kg cis-1,3-dichloropropene (Jones 1988b). Rats that received a single dermal application of 500 mg/kg Telone 1I®a developed lung congestion, and at 800 mg/kg, lung hemorrhage (Jones and Collier 1986b).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans following dermal exposure to 1,3-dichloropropene.

Gross necropsy revealed that rats that received a single dermal application of 800 mg cis-1,3-dichloropropene/kg had hemorrhage and ulceration of the glandular gastric mucosa (Jones 1988b). Similarly, rats that received a single dermal application of 800 mg/kg Telone II®a suffered hemorrhage of the stomach and congestion and hemorrhage of the intestines (Jones and Collier 1986b). No gastrointestinal effects were observed in rats that received 500 mg/kg cis-1,3-dichloropropene or 500 mg/kg Telone II®a.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans following dermal exposure to 1,3-dichloropropene.

Of six rabbits that died following dermal application of 500 mg/kg Telone C-17®, two had developed skeletal muscle hemorrhage underneath the site of application (Mizell et al. 1988b).

Hepatic Effects. No studies were located regarding hepatic effects in humans after dermal exposure to 1,3-dichloropropene.

Gross necropsy revealed abnormally dark livers in rats that received a single dermal application of 800 mg cis-1,3-dichloropropene/kg or more (Jones 1988b). The toxicological significance of this observation was not discussed. No other studies were located regarding hepatic effects in animals after dermal exposure to 1,3-dichloropropene.

Dermal/Ocular Effects. No studies were located regarding dermal or ocular effects in humans following dermal exposure to 1,3-dichloropropene.

Skin sensitization to 1,3-dichloropropene was noted in a 26-year-old male exposed during the manufacture of the soil fumigant DD-92® (Van Joost and de Jong 1988). Skin contact produced an itchy rash in this subject.

Acute dermal application of dilute or full strength Telone II®a or M-3993 rapidly produced erythema and edema in rats, rabbits, and guinea pigs (Carreon and Wall 1983; Jeffrey 1987c; Jones and Collier 1986b; Lichy and Olson 1975; Mizell 1988a). At concentrations of 200 mg/kg or more, necrosis and subcutaneous/skeletal muscle hemorrhage were observed (Jones and Collier 1986b; Mizell 1988a; Mizell et al. 1988b).

Telone 1I®a and Telone C-17® also produced a delayed-type hypersensitivity in guinea pigs (Carreon and Wall 1983; Jeffrey 1987a; Mizell 1988b).

Severe conjunctival irritation, cornea1 injury, and cornea1 opacity were observed after instillation of 0.1 mL Telone II®a or M-3993 into the conjunctival sacs of rabbits (Jeffrey 1987b; Lichy and Olson 1975).

2.2.3.3 Immunological Effects

Skin sensitization to DD-92® was noted as an itchy rash on the hands and feet of a 26-year-old male exposed during the manufacture of a soil fumigant (Van Joost and de Jong 1988). Positive patch tests for 1,3-dichloropropene confirmed the sensitization.

Delayed-type hypersensitivity reactions to Telone II®a and Telone C-17® were observed in guinea pigs (Carreon and Wall 1983; Jeffrey 1987a; Mizell 1988b). Guinea pigs also developed contact sensitization to cis-1,3-dichloropropene
(Jones 1988c).

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans after dermal exposure to 1,3-dichloropropene.

Rats that received single dermal applications of 500 mg cis-1,3-dichloropropene/kg or more were lethargic and had increased salivation (Jones 1988b). At 800 mg/kg or more, ptosis, hunched posture, pilo-erection, lethargy, and decreased respiration rate were noted. Ataxia was observed in this study at dose leve,ls of 1,300 mg/kg and 2,000 mg/kg (Jones 1988b). Rats that received a single dermal application of 1,300 mg/kg or more of Telone II®a became ataxic and lost the righting reflex, indicating neurological deficits (Jones and Collier 1986b). Several studies reported clinical signs in rats and rabbits that possibly indicate a neurological effect of 1,3-dichloropropene after dermal application. These signs included lethargy, salivation, lacrimation, and labored respiration (Jeffrey et al. 1987; Jones and Collier 1986b; Mizell et al. 1988).

No studies were located regarding the following effects in humans or animals after dermal exposure to 1,3-dichloropropene:

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding cancer in humans after dermal exposure to 1,3-dichloropropene.

1,3-Dichloropropene was not a tumor-initiator in mice treated with a single application of 122 mg per mouse, followed by repeated applications of the tumor-promoter, phorbol myristic acid, for 58 weeks. 1,3-Dichloropropene did not induce skin-papilloma formation in mice after dermal application of 122 mg per mouse three times weekly for 74 weeks (Van Duuren et al. 1979). Therefore, 1,3-dichloropropene does not appear able to initiate or induce skin tumors in mice.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

The detection of the N-acetyl-cysteine conjugate of 1,3-dichloropropene in the urine of four men 24 hours after field application of Telone II®a indicates that 1,3-dichloropropene is absorbed in humans after inhalation exposure (Osterloh et al. 1984).

Evidence from animal studies supports this observation in humans. Mixtures of cis and trans isomers of 1,3-dichloropropene were rapidly absorbed by rats after inhalation exposure (Stott and Kastl 1986). The rate of uptake in rats exposed to 30, 90, 300, or 900 ppm was 144±14, 307±13, 880±83, or 1810±76 nmol/minute, respectively. This corresponds to 82%, 65%, 66%, or 62% uptake, respectively. A decrease in the respiratory rate was observed in rats exposed to 90 ppm or more, which could account for the decrease in uptake at these concentrations. Steady-state blood levels were reached within 1 hour at 30 and 90 ppm and within 2-3 hours at 300 ppm, but did not reach steady state within 3, hours at 900 ppm. The increased length of time required to reach steady state at 300 and 900 ppm was likely a function of the observed decrease in respiratory rate. Nonlinear excretion kinetics also contributed to the decreased uptake observed at 300 and 900 ppm; disproportionate increases in the blood levels of cis-1,3-dichloropropene at 900 ppm and of

trans-1,3-dichloropropene at 300 and 900 ppm could indicate changes in distribution and/or metabolism.

Steady-state blood levels of the glutathione-conjugate of 1,3-dichloropropene were reached within 15 minutes in rats exposed to 78, 155, or 404 ppm Telone II®a, indicating that absorption was rapid (Fisher and Kilgore 1989).

2.3.1.2 Oral Exposure

No studies were located regarding absorption of 1,3-dichloropropene in humans after oral exposure.

1,3-Dichloropropene was well absorbed following gavage administration of ^{14}C-labeled cis- and/or trans-1,3-dichloropropene in rats (Climie et al. 1979; Hutson et al. 1971). Recovery of [^{14}C]cis-1,3-dichloropropene in 24-hour urine collections was 82%-84% in rats (Climie et al. 1979). Similarly, 82%-84% of ^{14}C-labeled cis-1,3-dichloropropene was recovered in urine, and 2%-3% was recovered in feces during a 96-hour urine collection period after gavage administration in rats (Hutson et al. 1971). In contrast, only 55%-60% of the ^{14}C-labeled trans-1,3-dichloropropene was recovered in the urine and 2% in the feces during the same period. These data indicate that both isomers of 1,3-dichloropropene are extensively absorbed by the oral route of exposure, which could lead to distribution throughout the body.

2.3.1.3 Dermal Exposure

No studies were located regarding the absorption of 1,3-dichloropropene after dermal exposure in humans or animals. The dermal LD_{50} for 1,3-dichloropropene in rabbits has been determined and indicates that this compound is absorbed by the dermal route of exposure (Lichy and Olson 1975).

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding the distribution of 1,3-dichloropropene after inhalation exposure in humans or animals.

2.3.2.2 Oral Exposure

No studies were located regarding distribution of 1,3-dichloropropene in humans after oral exposure.

Analysis of the distribution of radioactivity 48 hours after gavage administration of ^{14}C-cis/trans-1,3-dichloropropene to rats revealed essentially equal distribution of 1,3-dichloropropene or its metabolites to most organs and tissues (Waechter and Kastl 1988). The highest concentrations

of radioactivity were found in the nonglandular stomach and the urinary bladder. Lower concentrations of radioactivity were also found in blood, bone, brain, fat, heart, kidney, liver, lung, skeletal muscle, skin, spleen, ovaries, and testes.

2.3.2.3 Dermal Exposure

No studies were located regarding the distribution of 1,3-dichloropropene after inhalation exposure in humans or animals.

2.3.3 Metabolism

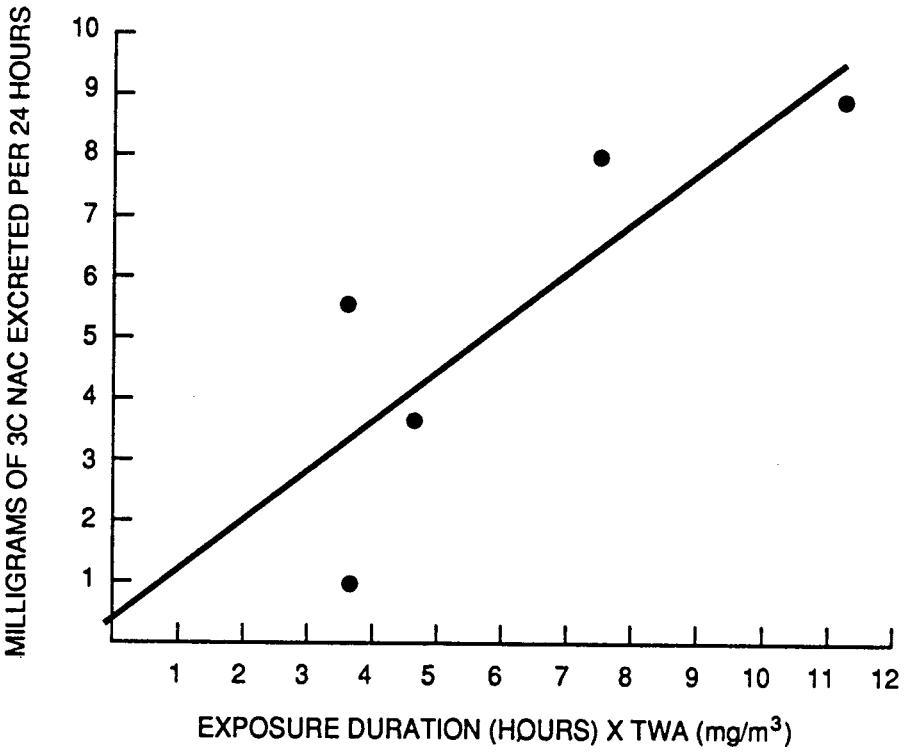
2.3.3.1 Inhalation Exposure

The N-acetyl-cysteine conjugate of cis-1,3-dichloropropene was detected in the urine of four men exposed occupationally to Telone II®a, indicating that glutathione conjugation is a metabolic pathway in humans (Osterloh et al. 1984). Exposure levels were monitored by personal dosimeters. A strong correlation was found between exposure levels of 1,3-dichloropropene and urinary excretion of the N-acetyl-cysteine conjugate (r-0.83). These data are presented in Figure 2-3.

1,3-Dichloropropene was rapidly metabolized to the glutathione conjugate in rats after inhalation exposure (Fisher and Kilgore 1989). The blood level of the glutathione conjugate reached a steady state of 116 nmol/mL within 15 minutes after exposure of rats to Telone 1I®a. The increase in blood levels of the glutathione conjugate correlated with the decrease in nonprotein sulfhydryl (glutathione) content of nasal tissues (Fisher and Kilgore 1988a). Glutathione levels in the kidney and liver were also decreased after inhalation exposure of rats to Telone II®a, but lung levels were not affected (Stott and Kastl 1986). The data indicate that conjugation with glutathione can occur in the nasal tissue, kidney, and liver. The glutathione conjugate of 1,3-dichloropropene is then converted to the mercapturic acid and acetylated for excretion as the N-acetyl-cysteine metabolite (Fisher and Kilgore 1988b).

The two isomers of 1,3-dichloropropene appear to be metabolized at different rates. Plateau blood levels of the cis and trans isomers were 0.085±0.024 and 0.12±0.03 µg/mL, respectively, in rats exposed to 30 ppm Telone II®a for 1 hour, and 0.20±0.04 and 0.26±0.03 µg/mL, respectively, in rats exposed to 90 ppm Telone II®a for 1 hour. Plateau blood levels reached after 2-3 hours in rats exposed to 300 ppm were 0.89±0.2 and 1.87±0.27 µg/mL for the cis and trans isomers, respectively (Stott and Kastl 1986). In vitro studies using a rat liver enzyme preparation revealed that the cis isomer was metabolized four to five times faster than the trans isomer (Climie et al. 1979).

FIGURE 2-3. Correlation of Exposure to 1,3-Dichloropropane with Urinary Excretion of the N-Acetyl Cysteine Metabolite*



*Derived from Osterloh et al. 1984

2.3.3.2 Oral Exposure

Orally administered 1,3-dichloropropene is also metabolized by conjugation with glutathione (Climie et al. 1979). Urine collected for 24 hours after oral administration of ^{14}C-labeled cis-1,3-dichloropropene in rats yielded 82%-84% of the radioactivity as the N-acetyl-cysteine conjugate of 1,3-dichloropropene. Two other urinary metabolites that accounted for 3% and 5% of the administered radioactivity were found but not identified (Climie et al. 1979). Tissue nonprotein sulfhydryl content was assayed in mice following a single gavage administration of 50 mg/kg cis- and trans-1,3-dichloropropene (Dietz et al. 1982). Decreased tissue nonprotein sulfhydryl levels were observed in the forestomach, glandular stomach, liver, and kidney, which indicated that glutathione conjugation occurred at these sites.

No differences were observed in the distribution or the rate and extent of metabolism or excretion of 1,3-dichloropropene after gavage administration between rats that received a single dose and rats that received repeated doses. Furthermore, no differences in distribution, metabolism, or excretion of 1,3-dichloropropene were observed between male and female rats (Waechter and Kastl 1988). The proposed metabolic pathway for 1,3-dichloropropene in rats is presented in Figure 2-4.

2.3.3.3 Dermal Exposure

No studies were located regarding metabolism of 1,3-dichloropropene after dermal exposure in humans or animals.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

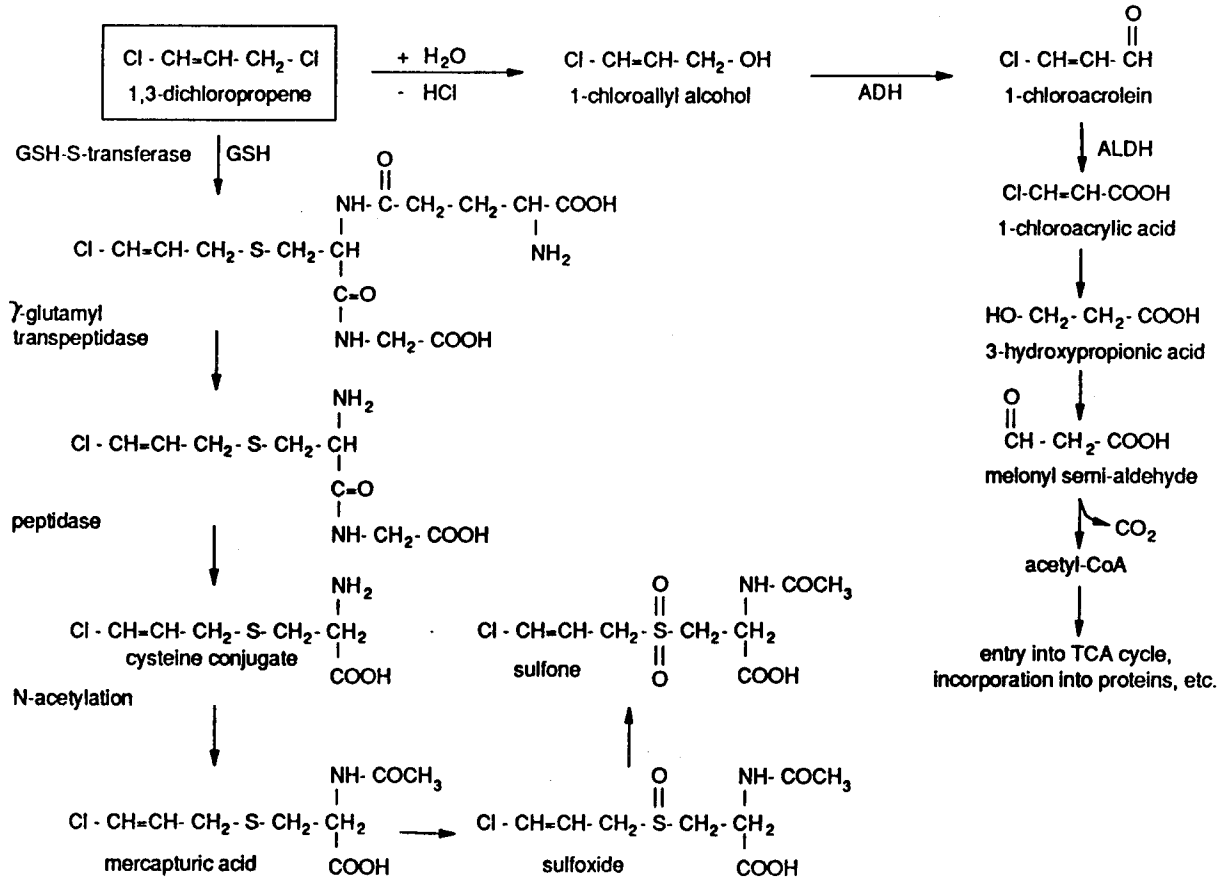
A strong correlation was reported for humans between occupational exposure to Telone II®a and urinary levels of the N-acetyl-cysteine conjugate of cis-1,3-dichloropropene (r=0.83) (Osterloh et al. 1984). Rats exposed by inhalation for 1 hour to 0, 40, 107, 284, 398, or 789 ppm Telone II®a excreted 0, 0.11, 0.49, 2.7, 3.7, or 4.0 µmol N-acetyl-cysteine conjugate/ml of urine in the 24 hours following exposure (Fisher and Kilgore 1988b). Uptake levels, however, were not measured, which precludes correlation with excretion.

2.3.4.2 Oral Exposure

No studies were located regarding excretion of 1,3-dichloropropene after oral exposure in humans.

Significant recoveries of ^{14}C-labeled 1,3-dichloropropene were reported in two studies with rats after oral exposure (Climie et al. 1979; Hutson et al. 1971). In both studies, 82%-84% of the administered cis isomer was

FIGURE 2-4. Proposed Metabolic Pathway for 1,3-Dichloropropene in the Rat



*Derived from Waechter and Kastl 1988

recovered as the mercapturic acid conjugate of 1,3-dichloropropene in a 24-hour collection of urine. Two other minor metabolites that accounted for 3% and 5% of the radioactivity were observed, but these metabolites were not identified (Climie et al. 1979). Comparison of the excretory pathways for the cis and trans isomers of 1,3-dichloropropene revealed that 82%-84% of the cis isomer was recovered as the mercapturic acid conjugate in the 24-hour urine collection; only 55%-60% of the trans isomer was recovered as the mercapturic acid conjugate in the urine (Hutson et al. 1971). A significant portion of the trans isomer was recovered as $^{14}CO_2$ (22%-25%). A smaller percentage of each isomer was recovered in the feces: 2%-3% of the cis and 2% of the trans isomer. Less than 2% of either compound remained in the carcass after 4 days (Hutson et al. 1971). These data indicate that neither isomer of 1,3-dichloropropene has a tendency to concentrate in the body.

2.3.4.3 Dermal Exposure

No studies were located regarding excretion of 1,3-dichloropropene after dermal exposure in humans or animals.

2.4 RELEVANCE TO PUBLIC HEALTH

Humans are most likely to be exposed to 1,3-dichloropropene in an occupational setting or in agricultural areas where this chemical is in use. 1,3-Dichloropropene is widely used in agriculture as a preplanting pesticide. Both inhalation and dermal exposure is possible during the application of 1,3-dichloropropene to fields or during the cleanup of an accidental spill. 1,3-Dichloropropene has been found in the water supplies of agricultural areas where it is used; therefore, oral exposure is possible.

Human health effects observed after accidental exposure at the site of a tank truck spill included headache, mucous membrane irritation, dizziness, chest discomfort, nausea, vomiting, abdominal discomfort, and malaise. Three men occupationally exposed to high concentrations of 1,3-dichloropropene developed hematological malignancies that may have been associated with the chemical. Skin sensitization to 1,3-dichloropropene has also been reported after exposure during the manufacture of a pesticide containing 1,3-dichloropropene.

The effects of 1,3-dichloropropene exposure observed in animals include death, damage to the nasal tissues, lungs, liver, kidneys, and urinary bladder. 1,3-Dichloropropene has also caused lung adenomas, stomach papillomas and carcinomas, neoplastic liver nodules, and urinary bladder carcinomas in animals.

The information on effects of acute inhalation exposure to 1,3-dichloropropene is limited to effects on respiratory and dermal irritation, and neurological and developmental effects. An acute inhalation MEL was not derived because the available NOAEL and LOAEL values for respiratory effects

(the end point on which intermediate- and chronic-duration MRLs are based) and for neurological and developmental effects are higher than or too close to acute inhalation LC_{50} values. Sufficient information is available on the health effects of 1,3-dichloropropene to derive MRLs for intermediate- and chronic-duration inhalation exposure. Based on a NOAEL of 10 ppm for histological changes in the nasal epithelium of rats (Coate 1979a), an intermediate-duration inhalation MRL of 0.003 ppm was calculated by adjusting the NOAEL for intermittent exposure, converting the adjusted NOAEL to an equivalent concentration in humans, and dividing the equivalent concentration by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). The LOAEL for effects on the nasal epithelium was 30 ppm (Coate 1979a). Nasal lesions also occurred in rats (Breslin et al. 1989) and mice (Coate 1979a) exposed to 90 ppm 1,3-dichloropropene for intermediate durations. No effects in other organs and tissues were observed in rats and mice exposed to 1,3-dichloropropene at 190 ppm (.Breslin et al. 1989; Coate 1979a; Linnett et al. 1988) or in dogs exposed to 3 ppm (Torkelson and Oyen 1977) for intermediate durations. Based on a NOAEL of 5 ppm for nasal epithelial hyperplasia of mice (Lomax et al. 1989), a chronic-duration inhalation MRL of 0.002 ppm was calculated by adjusting the NOAEL for intermittent exposure, converting the adjusted NOAEL to an equivalent concentration in humans, and dividing the equivalent concentration by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). The LOAEL for nasal epithelial changes was 20 ppm (Lomax et al. 1989). Rats exposed chronically to 60 ppm 1,3-dichloropropene had nasal epithelial degeneration (Lomax et al. 1989). Other than hyperplasia and hyperkeratosis of the forestomach in mice exposed to 60 ppm, no other effects were noted in rats or mice chronically exposed to 1,3-dichloropropene by inhalation.

An acute oral MRL was not derived because the available NOAEL and LOAEL values for systemic and neurological effects are higher than or too close to LD_{50} values. An intermediate-duration oral MRL was not derived because the available studies did not identify target organs or systems for this duration category. A chronic-duration oral MRL was not derived because hydronephrosis, a serious effect, was observed at the same dose level (50 mg/kg/day) that was a NOAEL value for all other systemic effects, except forestomach hyperplasia. The LOAEL for forestomach hyperplasia (25 mg/kg/day) was lower than the serious LOAEL for nephrosis, but forestomach hyperplasia is not an appropriate end point for the MRL because it represents a preneoplastic lesion. Both the rats and the mice developed forestomach papilloma and carcinoma at comparable doses in this study (NTP 1985).

Acute-, intermediate-, and chronic-duration dermal MRLs were not derived for 1,3-dichloropropene due to the lack of an appropriate methodology for the development of dermal MRLs.

Death. No deaths in humans have been reported after inhalation, oral, or dermal exposure to 1,3-dichloropropene. Several animal studies, however, have reported death as an end point after exposure by all routes. Available LC_{50} values for animals after inhalation exposure range from 253 ppm for Telone C-17® to 904 ppm for Telone II®a (Cracknell et al. 1983; Streeter and Lomax 1988; Streeter et al. 1987). Human exposures to such high concentrations are not likely near hazardous waste sites, but may occur accidentally or through faulty equipment during its application in agriculture. Seven of 10 human subjects could detect 1 ppm Telone II® and described the odor as noticeably fainter than 3 ppm (Torkelson and Oyen 1977). Therefore, evacuation from an area that contained 1,3-dichloropropenecontaminated air would be possible before exposure caused harm.

Workers who were involved in the agricultural application of 1,3-dichloropropene were exposed to concentrations under 1 ppm (Albrecht 1987; Maddy et al. 1980, 1982a; Osterloh et al. 1984). Therefore, exposure to 1,3-dichloropropene at concentrations that could cause death in humans is not likely in an occupational setting. Furthermore, because 1,3-dichloropropene is rapidly cleared from the body after inhalation exposure (Fisher and Kilgore 1989), it would not be expected to accumulate in the body after repeated exposure to low concentrations.

Systemic Effects

Respiratory Effects. Inhalation exposure to 1,3-dichloropropene causes marked respiratory effects in humans and animals. Humans exposed to 1,3-dichloropropene after a tank truck spill complained of mucous membrane irritation, chest pain, and cough (Flessel et al. 1978). Rats exposed to 1,3-dichloropropene had lung congestion, tracheal congestion, and fluid in the thoracic cavity (Cracknell et al. 1987). Atelectasis, emphysema, and/or pulmonary edema, and lung hemorrhage have been observed in rats exposed to 1,3-dichloropropene vapors (Streeter and Lomax 1988; Streeter et al. 1987). The most consistent pathological finding after inhalation exposure in animals was hyperplasia and/or degeneration of the nasal epithelium (Breslin et al. 1989; Lomax et al. 1989; Stott et al. 1988). Severe respiratory effects would not be expected in humans exposed occupationally to 1,3-dichloropropene, because measured exposure levels are lower than those that produced respiratory effects in animals. Occupational accidents, however, may result in harmful exposure levels. Near hazardous waste sites, humans would be aware of 1,3-dichloropropene-contaminated air because of the chemical's odor; measures to prevent respiratory effects could then be taken.

Oral exposure to 1,3-dichloropropene caused an increased incidence of bronchioalveolar adenomas in mice (NTP 1985). Similar neoplasms were not found in rats under the same exposure protocol. Reasons for the species difference are not clear, although it may have resulted from aspiration of 1,3-dichloropropene in the mice after gavage administration. Oral exposure of

rats has also resulted in lung hemorrhage at doses that were fatal. Oral exposure to 1,3-dichloropropene in an occupational setting is not likely. Nevertheless, 1,3-dichloropropene has been found in human mother's milk (Pellizzari et al. 1982), in drinking water supplies located where 1,3-dichloropropene has been in use (Yang 1986), and in municipal water supplies, indicating that oral exposure can occur from environmental contamination with 1,3-dichloropropene (Dowty et al. 1975a, 1975b). The levels detected from these sources, however, were far lower than those that produced neoplasms in mice.

Rats that received a single dermal application of 1,3-dichloropropene (500 or 800 mg/kg) developed lung congestion (500 mg/kg) and lung hemorrhage (800 mg/kg) (Jones and Collier 1986b). Whether these respiratory effects were a direct effect of 1,3-dichloropropene was not clear. Dermal exposure in humans is a likely route of exposure, particularly during field application or during cleanup of an accidental spill. Although no studies were located regarding respiratory effects in humans after dermal exposure, it is possible that adverse respiratory effects could occur.

Gastrointestinal Effects. Humans exposed to 1,3-dichloropropene after a tank truck spill complained of nausea and vomiting (Flessel et al. 1978), which indicates that gastrointestinal effects are possible. Mice exposed to 60 ppm Telone 11% for 2 years by inhalation developed hyperplasia and hyperkeratosis of the forestomach (Lomax et al. 1989). These gastrointestinal effects were not observed in rats under the same exposure protocol, nor were they observed in mice examined after 6 or 12 months of exposure. Gastrointestinal effects were not observed in other studies of inhalation exposure. Whether gastrointestinal effects would occur in humans after inhalation exposure to 1,3-dichloropropene during field application or at hazardous waste sites cannot be determined on the basis of the available data.

Although no studies were located regarding gastrointestinal effects in humans after oral exposure to 1,3-dichloropropene, animal studies indicate that humans who reside near hazardous waste sites or are occupationally exposed to 1,3-dichloropropene could suffer gastrointestinal effects if oral exposure were to occur. Chronic oral exposure of rats and mice to 1,3-dichloropropene produced neoplastic and preneoplastic lesions of the stomach (NTP 1985). An increased incidence of forestomach squamous cell papillomas and carcinomas was observed in rats and mice after 2 years of gavage administration of 1,3-dichloropropene. These lesions were accompanied by an increased incidence of forestomach basal cell or epithelial cell hyperplasia.

Dermal exposure of rats to 1,3-dichloropropene caused stomach hemorrhage and intestinal congestion and hemorrhage (Jones 1988b; Jones and Collier 1986b). Whether these effects were directly related to 1,3-dichloropropene exposure was not discussed. Thus, the risk of gastrointestinal effects

following dermal exposure in humans who reside near hazardous waste sites or are occupationally exposed cannot be determined.

Hematological Effects. Limited human data suggest that hematological malignancies may be associated with 1,3-dichloropropene exposure but other hematological effects have not been reported. No hematological effects have been observed in numerous animal studies by inhalation or oral exposure (see Section 2.2), even in studies that included extensive hematological analysis. The available data indicate that nonneoplastic hematological effects are probably not associated with 1,3-dichloropropene exposure.

Musculoskeletal Effects. Musculoskeletal effects after 1,3-dichloropropene exposure have not been reported in humans. A single study described skeletal muscle hemorrhage after dermal application of large amounts of 1,3-dichloropropene in rabbits (Mizell et al. 1988). It is possible that dermal exposure to large amounts of 1,3-dichloropropene could have similar effects in humans.

Hepatic Effects. Hepatic effects in humans after 1,3-dichloropropene exposure have not been reported. Rats and mice did not develop hepatic lesions attributable to 1,3-dichloropropene after 24 months or less of inhalation exposure (Coate 1979b; Lomax et al. 1989; Parker et al. 1982; Stott et al. 1988). The only nonneoplastic hepatic effects reported in animals were mottled dark livers in rats after acute oral or dermal exposure (Jones 1988b; Jones and Collier 1986a) and increased liver weight in rats after exposure for 13 weeks (Til et al. 1973). On the basis of these animal data, it is possible that minimal adverse hepatic effects could occur in humans orally exposed to 1,3-dichloropropene that had leached into drinking water in agricultural areas or near hazardous waste sites. It is less likely that hepatic effects would be associated with inhalation exposure.

Renal Effects. No data are available regarding the renal effects of 1,3-dichloropropene exposure by any route in humans. Gross and histopathological evaluation of rats and mice exposed to 1,3-dichloropropene by inhalation for up to 2 years revealed no kidney lesions attributable to the chemical (Coate 1979b; Lomax et al. 1989; Parker et al. 1982; Stott et al. 1988). Urinary bladder hyperplasia, however, was a consistent finding in mice exposed to 1,3-dichloropropene by inhalation for up to 2 years (Lomax et al. 1989; Stott et al. 1988). Oral administration of 1,3-dichloropropene to mice also caused urinary bladder hyperplasia (NTP 1985). Similar lesions were not observed in rats under the same protocol. These data indicate that urinary tract effects may occur in humans after inhalation or oral exposure to 1,3-dichloropropene.

Dermal/Ocular Effects. Dermal application of 1,3-dichloropropene consistently produces erythema and edema in rats, rabbits, and guinea pigs (Carreon and Wall 1983; Jeffrey 1987c; Jones and Collier 1986b; Lichy and Olson 1975; Mizell 1988a). Higher concentrations can also produce necrosis

and subcutaneous or skeletal muscle hemorrhage (Jones and Collier 1986; Mizell 1988a; Mizell et al. 1988). Such effects would also be expected to occur by the dermal route in humans.

Serious ocular effects have been observed in rabbits that had 1,3-dichloropropene instilled into the conjunctival sac. These effects include conjunctival irritation, cornea1 irritation, and cornea1 opacity (Jeffrey 1987b; Lichy and Olson 1975). Inhalation exposure may also result in eye irritation. Clinical signs noted in rabbits and rats exposed to 1,3-dichloropropene by inhalation included palpebral closure and lacrimation (Jeffrey et al. 1987; Jones and Collier 1986; Mizell et al. 1988). Therefore, humans who reside near hazardous waste sites or are occupationally exposed to 1,3-dichloropropene could suffer eye and/or skin irritation.

Immunological Effects. A delayed-type hypersensitivity to 1,3-dichloropropene has been described in humans (Van Joost and de Jong 1988). Delayed-type hypersensitivity or contact sensitization has also been demonstrated in guinea pigs (Carreon and Wall 1983; Jeffrey 1987a; Jones 1988c; Mizell et al. 1988b). These data also indicate that immunological effects may result from dermal exposure to 1,3-dichloropropene.

Neurological Effects. No neurological effects were observed in humans exposed to 1,3-dichloropropene at levels that were high enough to require medical attention (Markovitz and Crosby 1984). Nausea and vomiting, however, were clinical signs noted in humans exposed to 1,3-dichloropropene after a tank truck spill (Flessel et al. 1978). These symptoms may indicate neurological effects. Ataxia of the hindlimbs and loss of the righting reflex were observed in pregnant rabbits exposed by inhalation to 300 ppm 1,3-dichloropropene during gestation days 6-18 (Kloes et al. 1983). No neurological signs were noted in rabbits exposed to 50 or 150 ppm Telone 1I®a in the same study. Dermal application of 1,300 mg/kg Telone II®a caused ataxia and loss of the righting reflex in rats (Jones and Collier 1986b). For humans who are exposed occupationally or are near hazardous waste sites, these data indicate that neurological effects may accompany 1,3-dichloropropene exposure.

Developmental Effects. No data were located regarding developmental effects in humans following exposure to 1,3-dichloropropene by any route. Animal studies indicate that inhalation exposure to 1,3-dichloropropene is not fetotoxic or teratogenic in rats or rabbits (Breslin et al. 1989; Hanley et al. 1987). No adverse developmental effects were observed in rats exposed to Telone 11% for two generations (Breslin et al. 1989). These data indicate that developmental effects would probably not occur in humans exposed to 1,3-dichloropropene.

Reproductive Effects. No data were located regarding reproductive effects in humans after exposure to 1,3-dichloropropene by any route. No

reproductive effects were observed in rats exposed by inhalation to 1,3-dichloropropene for two generations. Male and female rats evaluated for libido, fertility, and estrus cycling were not adversely affected by inhalation exposure to 1,3-dichloropropene (Linnett et al. 1988). Gross and histologic examination of reproductive tissues and organs revealed no lesions attributable to 1,3-dichloropropene exposure by inhalation or gavage in rats or mice (Breslin et al. 1989; Hanley et al. 1987; Linnett et al. 1988; NTP 1985; Parker et al. 1982; Stott et al. 1988;). These data indicate that reproductive effects would probably not result from 1,3-dichloropropene exposure in humans. Based on oral exposure studies with rats, however, 1,3-dichloropropene or its metabolites are distributed to reproductive tissues including the ovaries and testes (Waechter and Kastl 1988).

Genotoxic Effects. No studies were located regarding genotoxic effects in humans or animals after inhalation, oral, or dermal exposure to 1,3-dichloropropene. In a Drosophila melanogaster feeding study, however, 1,3-dichloropropene produced sex-linked recessive lethal mutations (Valencia et al. 1987). Genotoxicity studies of 1,3-dichloropropene in vitro test systems are described in Table 2-4.

Several groups have reported that 1,3-dichloropropene is mutagenic in vitro with and without metabolic activation in Salmonella tvnhimurium (Creedy et al. 1984; De Lorenzo et al. 1977; Eder et al. 1982a, 1982b; Haworth et al. 1983; Neudecker and Henschler 1986; Neudecker et al. 1977; Stolzenberg and Hine 1980; Vithayathil et al. 1983). In contrast, 1,3-dichloropropene purified on silic acid columns was not mutagenic (Talcott and King 1984). Silic acid removes polar impurities, which, when added back to the purified 1,3-dichloropropene, restore the mutagenic activity (Talcott and King 1984). An independent group confirmed these observations and also found that the impurities alone were mutagenic (Watson et al. 1987).

In mammalian test systems, 1,3-dichloropropene triggered unscheduled DNA synthesis in HeLa cells (Eder et al. 1987; Schiffman et al. 1983), sister chromatid exchange in Chinese hamster V79 cells (von der Hude et al. 1987), and Chinese hamster ovary cells (Loveday et al. 1989), and mitotic aberrations in Chinese hamster lung cells (Sasaki et al. 1988).

These data indicate that exposure of humans to formulations of 1,3-dichloropropene may result in genotoxic effects.

Cancer. Evidence for the carcinogenicity of 1,3-dichloropropene in humans is very limited. Clinical reports describing the development of neoplasms in three men following inhalation (and possibly dermal) exposure suggest, however, that 1,3-dichloropropene might cause cancer in humans. Two of the men were exposed to 1,3-dichloropropene during the cleanup of a tank truck spill. Six years later, both men simultaneously developed and succumbed to histiocytic lymphoma that was refractory to treatment (Markovitz and Crosby

TABLE 2-4. Genotoxicity of 1,3-Dichloropropene *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Isomer/ formulation
Prokaryotic organisms:					
Salmonella typhimurium (TA100)	Reverse mutation	+	+	Creedy et al. 1984	cis, trans
S. typhimurium (TA1978)	Reverse mutation	+	-	DeLorenzo et al. 1977	Telone DD[●]
S. typhimurium (TA1535)	Reverse mutation	+	+	DeLorenzo et al. 1977	Telone DD[●]
S. typhimurium (TA100)	Reverse mutation	+	+	DeLorenzo et al. 1977	Telone DD[●]
S. typhimurium (TA1537)	Reverse mutation	-	-	DeLorenzo et al. 1977	Telone DD[●]
S. typhimurium (TA98)	Reverse mutation	-	-	DeLorenzo et al. 1977	Telone DD[●]
S. typhimurium (TA1535)	Reverse mutation	+	+	DeLorenzo et al. 1977	cis, trans
S. typhimurium (TA1978)	Reverse mutation	+	+	DeLorenzo et al. 1977	cis, trans
S. typhimurium (TA100)	Reverse mutation		+	DeLorenzo et al. 1977	cis, trans
S. typhimurium (TA100)	Reverse mutation	+	+	Eder et al. 1982a	cis, trans
S. typhimurium (TA100)	Reverse mutation	+	+	Eder et al. 1982b	cis, trans
S. typhimurium (TA100)	Reverse mutation	+	+	Haworth et al. 1983	cis, trans
S. typhimurium (TA1535)	Reverse mutation	+	+	Haworth et al. 1983	cis, trans
S. typhimurium (TA1537)	Reverse mutation	+	+	Haworth et al. 1983	cis, trans
S. typhimurium (TA98)	Reverse mutation	+	+	Haworth et al. 1983	cis, trans
S. typhimurium (TA1535)	Reverse mutation	+	+	Neudecker et al. 1977	cis, trans
S. typhimurium (TA1537)	Reverse mutation	+	+	Neudecker et al. 1977	cis, trans
S. typhimurium (TA1538)	Reverse mutation	+	+	Neudecker et al. 1977	cis, trans
S. typhimurium (TA100)	Reverse mutation	+	+	Neudecker et al. 1980	cis, trans
S. typhimurium (TA100)	Reverse mutation	+	+	Neudecker and Henschler 1986	cis, trans
S. typhimurium (TA100)	Reverse mutation	+	+	Stolzenberg and Hine 1980	cis, trans
S. typhimurium (TA100)	Reverse mutation	No data	-	Talcott and King 1984	Not pure[a]
	Reverse mutation	No data	-	Talcott and King 1984	Purified[a]
	Reverse mutation	No data	+	Talcott and King 1984	Not pure[b]
	Reverse mutation	No data	-	Talcott and King 1984	Purified[b]
	Reverse mutation	No data	+	Talcott and King 1984	Not pure[c]
	Reverse mutation	No data	-	Talcott and King 1984	Purified[c]
	Reverse mutation	No data	+	Talcott and King 1984	Not pure[d]
	Reverse mutation	No data	-	Talcott and King 1984	Purified[d]
	Reverse mutation	No data	+	Talcott and King 1984	cis + trans[e]
S. typhimurium (TA98)	Reverse mutation	No data	+	Vithayathil et al. 1983	cis, trans
S. typhimurium (TA98)	Rifampicin resistance	No data	+	Vithayathil et al. 1983	cis, trans
Escherichia coli (PQ37)	DNA damage	No data	+	Von der Hude et al. 1988	cis, trans
S. typhimurium (TA100)	Reverse mutation	+	+	Watson et al. 1987	Not pure[f]
	Reverse mutation	-	-	Watson et al. 1987	Purified[f]
	Reverse mutation	+	+	Watson et al. 1987	Impurities[g]

TABLE 2-4 (Continued)

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Isomer/ formulation
Eukaryotic organisms:					
HeLa cells	Unscheduled DNA synthesis	No data	+	Eder et al. 1987	cis, trans
HeLa cells	Unscheduled DNA synthesis	No data	+	Schiffman et al. 1983	cis, trans
Chinese hamster ovary cells	Sister chromatid exchange	+	+	Loveday et al. 1989	Telone II®b
Chinese hamster ovary cells	Chromosomal aberrations	-	-	Loveday et al. 1989	Telone II®b
Chinese hamster V79 cells	Sister chromatid exchange	-	+	von der Hude et al. 1987	cis, trans
Chinese hamster lung cells	Mitotic aberrations	+	+	Sasaki et al. 1988	cis + trans

[a]cis and trans 1,3-Dichloropropene supplied by K&K Laboratories
[b]cis and trans 1,3-Dichloropropene supplied by Pfaltz and Bauer, Inc.
[c]Low-boiling 1,3-Dichloropropene supplied by K&K Laboratories
[d]High-boiling 1,3-Dichloropropene supplied by K&K Laboratories
[e]Pfaltz and Bauer 1,3-dichloropropene was purified; impurities were then added back (refluxed) for the mutagenicity assay.
[f]cis-1,3-Dichloropropene
[g]Impurities from purified cis-1,3-dichloropropene

+ = positive response; - = negative response

1984). The same report described a farmer who developed acute myelomonocytic leukemia after being exposed to 1,3-dichloropropene while applying the chemical to his fields. This leukemia was also refractory to treatment, and the man died approximately 1 year later.

Evidence for carcinogenicity in animals is available. Rats that received 1,3-dichloropropene (Telone II®a) by gavage developed an increased incidence of forestomach squamous cell papillomas and carcinomas, liver neoplastic nodules, thyroid adenomas and carcinomas, and adrenal gland pheochromocytomas (NTP 1985). The increase in stomach neoplasms was accompanied by an increase in forestomach basal cell hyperplasia. Similarly, mice that received 1,3-dichloropropene (Telone II®a) by gavage developed an increased incidence of forestomach squamous cell papillomas and carcinomas (NTP 1985). Mice also developed an increased incidence of urinary bladder transitional cell carcinomas and lung adenomas and carcinomas. These neoplastic changes were accompanied by an increase in forestomach epithelial cell hyperplasia and urinary bladder hyperplasia. How much the epichlorohydrin component (1%) of Telone II®a contributes to the development of papillomas and carcinomas of the forestomach is not known. Although oral administration of epichlorohydrin has produced papillomas and carcinomas of the forestomach in male mice (NTP 1989), it is doubtful that Telone II®a contained enough epichlorohydrin for the tumor response to be due solely to epichlorohydrin.

Two-year inhalation exposure to 1,3-dichloropropene also produced neoplastic changes in mice but not rats (Lomax et al. 1989). A statistically significant, dose-related increase in bronchioalveolar adenomas was observed in the high dose males. Hyperplastic changes were also observed, including respiratory epithelium hyperplasia, urinary bladder hyperplasia, and hyperplasia and hyperkeratosis of the forestomach in male and female mice. Similar hyperplastic changes were not observed in rats under the same exposure protocol (Lomax et al. 1989). In contrast, other studies conducted over shorter exposure periods found significant increases in nasal epithelial hyperplasia in rats or mice (Breslin et al. 1989; Lomax et al. 1989; Stott et al. 1988). Whether these hyperplastic changes were preneoplastic is not clear, because nasal neoplasms were not found in rats or mice after longer exposure periods (Lomax et al. 1989).

In contrast to the inhalation and oral studies, 1,3-dichloropropene did not initiate or promote tumor formation in mice after dermal application for 58 or 74 weeks, respectively. Subcutaneous injection of 1,3-dichloropropene did, however, cause sarcomas at the injection site in mice (Van Duuren et al. 1979).

The animal data, along with suggestive data in humans, indicate that 1,3-dichloropropene is reasonably anticipated to cause cancer in humans.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism, (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to 1,3-dichloropropene are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by 1,3-dichloropropene are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to 1,3-Dichloropropene

Inhalation exposure to various concentrations of 1,3-dichloropropene correlated well with the urinary level of the N-acetyl cysteine (mercapturic acid) metabolite in humans. Urinary excretion of the N-acetyl cysteine metabolite was measured in four men occupationally exposed to technical-grade 1,3-dichloropropene (Telone IIea). Exposure levels were monitored by personal dosimeters. A strong correlation was found between exposure levels of 1,3-dichloropropene and urinary excretion of the N-acetyl-cysteine metabolite (r=0.83, see Figure 2-3 in Section 2.3.3) (Osterloh et al. 1984).

Blood levels of the glutathione-conjugate of 1,3-dichloropropene might also be used as a biomarker. Steady-state levels of the glutathione-conjugate were reached within 15 minutes in rats exposed to 78, 155, or 404 ppm (Fisher and Kilgore 1989). In this study, however, the correlation between exposure and blood levels was not calculated.

1,3-Dichloropropene is rapidly cleared from the body. The elimination half-time, determined after a l-hour inhalation exposure in rats, was 17 hours (Fisher and Kilgore 1989). Furthermore, less than 2% of the 1,3-dichloropropene administered by gavage to rats remained in the carcass after 4 days (Hutson et al. 1971). These data indicate that 1,3-dichloropropene does not concentrate in the body. Therefore, biomarkers based on tissue or blood levels of 1,3-dichloropropene are of limited value in assessing long-term exposure.

2.5.2 Biomarkers Used to Characterize Effects Caused by 1,3-Dichloropropene

No specific quantifiable biomarkers that characterize effects caused by 1,3-dichloropropene were identified. Consistent findings in animal studies include hyperplasia and/or degeneration of portions of the nasal epithelium after inhalation exposure, hyperplasia and/or neoplastic changes in the forestomach after oral exposure, and erythema/edema after dermal exposure. These are nonspecific effects and are, therefore, of little value as biomarkers.

2.6 INTERACTIONS WITH OTHER CHEMICALS

No studies were located regarding the interaction of 1,3-dichloropropene with other chemicals to produce health effects. 1,3-Dichloropropene is widely used as a preplanting soil fumigant for the control of parasitic nematodes. The commercial product used in agriculture contains a mixture of the cis and trans isomers in approximately equal proportions, as well as stabilizers including 1,2-dichloropropane and epichlorohydrin or epoxidized soybean oil. Occupational exposure would most likely occur to this mixture. Whether interactions occur between 1,3-dichloropropene and other components is not known.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

No data were located regarding populations that are unusually susceptible to the toxicity of 1,3-dichloropropene; however, glutathione availability is critical for detoxification. Depletion of glutathione pools may enhance or decrease the toxicity of 1,3-dichloropropene depending on the target organ (see Section 2.8). Glutathione pools could be depleted by repeated exposures to 1,3-dichloropropene or other xenobiotics that are metabolized in whole or in part by glutathione-dependent pathways. Urinary excretion of the mercapturic acid of 1,3-dichloropropene is the primary excretory pathway; therefore, kidney disease or deficiencies in the mercapturic acid transport system may also enhance the toxicity of 1,3-dichloropropene.

2.8 MITIGATION OF EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 1,3-dichloropropene. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to 1,3-dichloropropene. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice,

Recommendations have been made for managing and treating persons exposed to 1,3-dichloropropene (Bronstein and Currance 1988; Stutz and Janusz 1988). Initially, the exposed persons are removed from the contaminated area, and contaminated clothing is removed and isolated. Exposed skin is decontaminated by immediately washing with copious amounts of soapy water to insure appropriate dilution of the chemical. Contaminated eyes are thoroughly flushed with water. If the victim is in respiratory distress, ventilation assistance is provided, and oxygen administered. If oral exposure occurred recently, the victim is given water or milk to dilute the chemical and activated charcoal to adsorb the chemical. Emetics are not administered (Bronstein and Currance 1988). Please refer to Bronstein and Currance (1988) and Stutz and Janusz (1988) for more complete information on treatment of specific symptoms.

No specific information was located regarding the mitigation of effects of 1,3-dichloropropene once it has entered the bloodstream. The major effects of inhalation exposure to 1,3-dichloropropene are irritation and degenerative effects on the nasal and respiratory epithelium, and hyperplasia of the urinary bladder. The major effects of oral exposure are stomach irritation, hyperplasia, and hyperkeratosis, and mild liver and kidney effects. Studies on the metabolism of 1,3-dichloropropene indicate that a major pathway occurs via conjugation of 1,3-dichloropropene with glutathione resulting in the excretion of mercapturic acids and N-acetyl-cysteine conjugates (see Section 2.3.3). Inhalation exposure of rats to 1,3-dichloropropene resulted in

decreased levels of glutathione in the nasal tissue, kidney, and liver (Fisher and Kilgore 1988a). Oral exposure of mice to 1,3-dichloropropene resulted in decreased levels of glutathione in the forestomach, glandular stomach, liver, and kidney (Dietz et al. 1982). The decrease in glutathione levels in these tissues indicates that conjugation can occur in these tissues. If conjugation with glutathione represents a detoxification mechanism, it would seem likely that the nasal tissue and stomach damage occurs prior to conjugation. However, if 1,3-dichloropropene were detoxified in the kidney by conjugation with glutathione, it is difficult to explain the observed effects on the urinary bladder. One possible explanation is that glutathione conjugation in the kidney becomes saturated, allowing parent 1,3-dichloropropene to exert an effect. It is also possible that conjugation with glutathione could act as a toxifying mechanism. If this were the case for 1,3-dichloropropene, agents that deplete glutathione could protect against harmful effects of 1,3-dichloropropene. These agents, however, would have to be administered very soon after exposure occurred.

2.9 ADEQUACY OF THE DATABASE

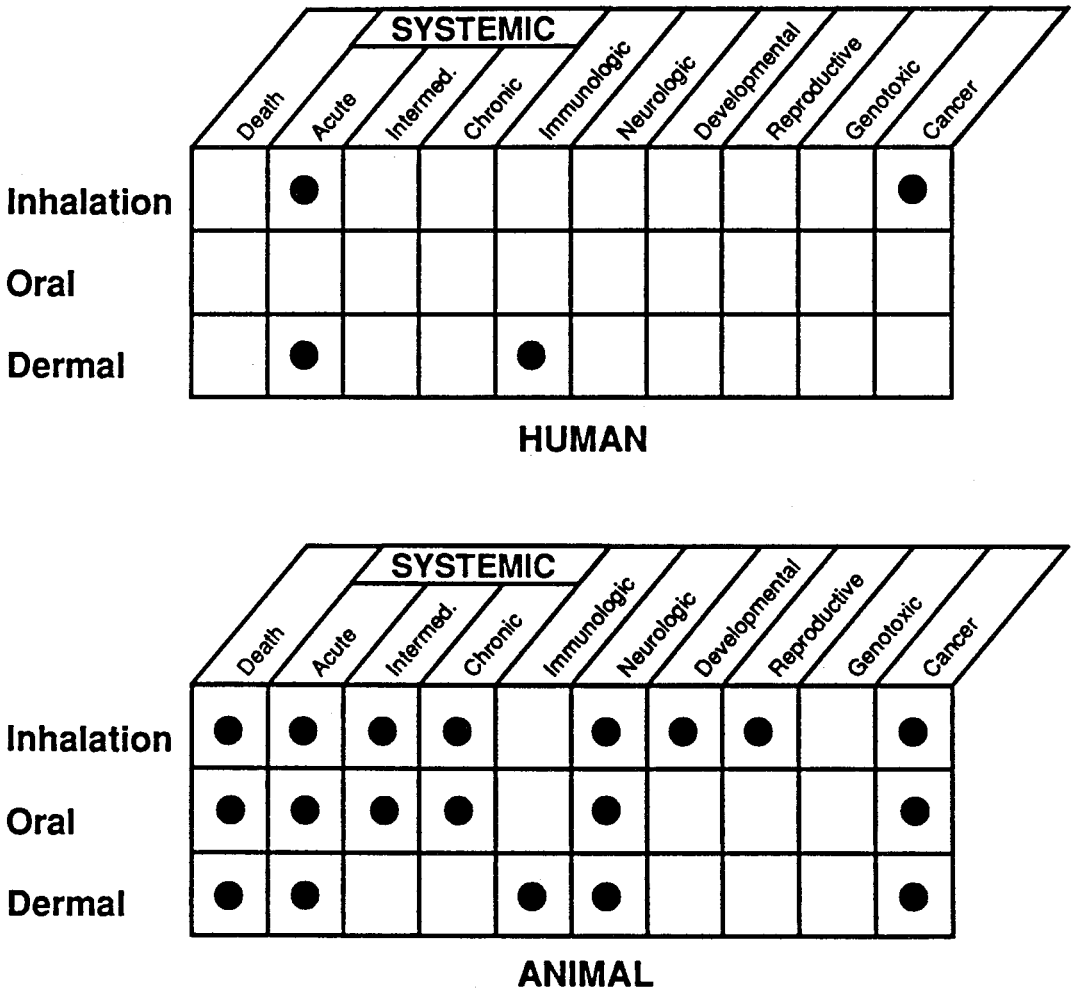
Section 104(i)(5) of CERCLA as amended directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,3-dichloropropene is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,3-dichloropropene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing Information on Health Effects of 1,3-Dichloropropene

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,3-dichloropropene are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,3-dichloropropene. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information (i.e., data gaps that must necessarily be filled).

FIGURE 2-5. Existing Information on Health Effects of 1,3-Dichloropropene



Existing information regarding the health effects of 1,3-dichloropropene in humans is limited (Figure 2-5). No information was located regarding death in humans after inhalation, oral, or dermal exposure. Acute systemic effects were reported after inhalation and possible dermal exposure to 1,3-dichloropropene. No information was located regarding systemic effects in humans after intermediate or chronic duration exposures by any route. A case of delayed-type hypersensitivity after dermal exposure indicates that 1,3-dichloropropene may have immunologic effects. A clinical report that discussed a possible role for 1,3-dichloropropene in chemical carcinogenesis was located. No studies were located regarding neurological, developmental, reproductive, or genotoxic effects in humans after exposure to 1,3-dichloropropene
by any route.

LC_{50}, and LD_{50} values for 1,3-dichloropropene have been determined in rats for inhalation exposure and oral exposure, and in rats and rabbits after dermal exposure. Systemic effects of 1,3-dichloropropene in animals have been described for all routes of exposure. Development of delayed-type hypersensitivity after dermal exposure indicates that 1,3-dichloropropene has immunologic effects. Neurological effects have been observed in animals after inhalation or dermal exposure. Developmental toxicity has been assessed in pregnant rats and rabbits after inhalation exposure. Reproductive toxicity has been assessed through comprehensive histological examinations of reproductive organs and tissues and in two-generation inhalation studies. The carcinogenicity of 1,3-dichloropropene has been assessed after exposure by all routes (Lomax et al. 1989; NTP 1985; Van Duuren et al. 1979).

2.9.2 Data Needs

Information regarding the health effects of exposure to pure 1,3-dichloropropene is very limited. Virtually all toxicological studies to date have tested various commercial formulations of 1,3-dichloropropene. Many of the components of these commercial formulations alone produce serious adverse health effects; therefore, future research efforts to assess the toxicity of 1,3-dichloropropene should include assessment of the pure chemical.

Acute-Duration Exposure. Data regarding human exposures to 1,3-dichloropropene are limited to clinical reports describing isolated cases of non-Hodgkin's (histiocytic) lymphoma and acute myelomonocytic leukemia after inhalation exposure (Markovitz and Crosby 1984), delayed-type hypersensitivity after dermal exposure (Van Joost and de Jong 1988), and nonspecific clinical signs such as headache, nausea, vomiting, fatigue, impotence, and malaise after inhalation (and possibly dermal) exposure. Respiratory symptoms such as chest discomfort, breathing difficulty, coughing, and mucous membrane irritation (Flessel et al. 1978; Markovitz and Crosby 1984) indicate that the respiratory system is a target in humans. Animal studies of acute-duration exposure describe nonspecific clinical signs

including lethargy, labored breathing, salivation, lacrimation, palpebral closure, and diarrhea. The primary target organ in animals after acute inhalation is also the respiratory tract. Lung hemorrhage and congestion, atelectasis, emphysema, pulmonary edema, and tracheal congestion have been observed (Cracknell et al. 1987; Streeter and Lomax 1988; Streeter et al. 1987). The available NOAEL and LOAEL values for respiratory effects (the end point on which intermediate- and chronic-duration MELs are based) and for neurological and developmental effects are higher than or too close to acute inhalation LC_{50} values, precluding the derivation of an MRL for acute inhalation exposure.

Information regarding the effects in humans of acute oral exposure to 1,3-dichloropropene is lacking, Acute oral studies in rats have identified the stomach, lungs, and possibly the liver and kidney as targets (Jones 1988a; Jones and Collier 1986a; Mizell et al. 1988a). An acute oral MRL was not derived because the available NOAEL and LOAEL values for systemic and neurological effects are higher than or too close to LD_{50} values.

Dermal exposure of humans to 1,3-dichloropropene has produced delayedtype hypersensitivity (Van Joost and de Jong 1988). Delayed-type hypersensitivity to 1,3-dichloropropene has also been observed in animals (Carreon and Wal 1983; Jeffrey 1987c; Mizell 1988b). Animal studies have shown that 1,3-dichloropropene causes erythema/edema, necrosis, exfoliation, and subcutaneous hemorrhage when applied dermally (Carreon and Wall 1983; Jeffrey 1987c; Jones and Collier 1986b; Lichy and Olson 1975; Mizell et al. 1988a, 1988b). Data regarding systemic toxicity in animals are limited. Hemorrhage of the lungs and glandular stomach was reported in a few studies (Jones 1988b; Jones and Collier 1986b).

Information on the distribution of 1,3-dichloropropene following oral, inhalation, and dermal exposure is not available to help identify other target organs across routes of exposure. Intermediate and chronic duration studies in rats and mice, which included extensive histological examinations, have identified targets of inhalation and oral exposure. Additional acute studies by all routes should focus on histological examinations of major organs and tissues including the lungs, liver, kidneys, stomach, and urinary bladder, as well as the determination of threshold doses. This information is important because populations near hazardous waste sites might be exposed to 1,3-dichloropropene for brief periods.

Intermediate-Duration Exposure. Data are not available that identify target organs in humanx after intermediate-duration exposure to 1,3-dichloropropene by any route.

Animal studies indicate that the primary target organs of 1,3-dichloropropene toxicity after intermediate-duration inhalation exposure are the respiratory tract and lungs, kidneys, and urinary bladder (Breslin et

al. 1989; Coate 1979a; Lomax et al. 1989; Stott et al. 1988). Nasal hyperplasia, bronchioalveolar adenomas, cloudy swelling of the kidneys, hydronephrosis, and urinary bladder hyperplasia have been observed. These observations have been made after extensive gross and histopathological examination. An intermediate inhalation MRL based on respiratory effects in rats has been calculated, An intermediate-duration oral MRL was not derived because the available studies did not identify target organs or systems for this duration category.

No information on target organs other than the skin (Jeffrey 1987a) was located for intermediate duration dermal exposure. No distribution data following inhalation, oral, or dermal exposure were located to help identify target organs of dermal exposure. An intermediate-duration dermal study in animals that examined organs other than skin should help identify the possible effects of dermal exposure to internal tissues. Because 1,3-dichloropropene is a component of a soil fumigant, contact with soil is one way that dermal exposure of humans could occur. Furthermore, 1,3-dichloropropene may be present in the soil at hazardous waste sites, where residents may be exposed for intermediate durations.

Chronic-Duration Exposure and Cancer. There is no information in humans to identify target organs following chronic exposure by inhalation, oral, or dermal routes.

The chronic toxicity of 1,3-dichloropropene has been assessed in two animal studies: a 2-year inhalation exposure of rats and mice (Lomax et al. 1989), and a 2-year gavage study also ,in rats and mice (NTP 1985). Hyperplasia of the nasal epithelium was the only nonneoplastic toxic effect observed in rats after inhalation exposure. In contrast, mice suffered nasal epithelial hyperplasia, degeneration of the olfactory neuroepithelium, an increased incidence of bronchioalveolar adenomas, and hyperplasia and hyperkeratosis of the forestomach. Nonneoplastic and preneoplastic lesions observed in rats after a 2-year gavage study included hyperkeratosis and basal cell hyperplasia of the forestomach and pancreatic periarteritis. In mice following gavage exposure, the nonneoplastic and preneoplastic lesions included forestomach epithelial cell hyperplasia, kidney hydronephrosis, and urinary bladder hyperplasia. The data from these two studies, which included comprehensive histological examinations, are sufficient to identify the respiratory tract as the primary target organ of chronic toxicity after inhalation exposure, and the forestomach, kidney, and urinary bladder after oral exposure. Furthermore, these data are sufficient to derive a chronic inhalation MRL based on respiratory effects in mice. The data available for chronic oral exposure are not appropriate for derivation of a chronic oral MRL, because hydronephrosis, a serious effect, was observed at the same dose level that was a NOAEL value for all other systemic effects, except forestomach hyperplasia. The LOAEL for forestomach hyperplasia was lower than the serious LOAEL for nephrosis, but forestomach hyperplasia is not an

appropriate end point for the MRL because it represents a preneoplastic lesion. Both the rats the mice developed forestomach papilloma and carcinoma at comparable doses in this study (NTP 1985). Neither studies regarding effects of chronic-duration dermal exposure nor distribution data to identify possible targets of exposure to 1,3-dichloropropene by this route of exposure were located.

Chronic-duration dermal exposure of humans who reside near a hazardous waste site or are occupationally exposed is likely. Therefore, a chronicduration study in animals may be warranted.

A clinical report describing three men who developed lymphoma or leukemia (Markovitz and Crosby 1984) suggests a carcinogenic potential for 1,3-dichloropropene in humans. The carcinogenicity of 1,3-dichloropropene was assessed in a 2-year inhalation study of rats and mice (Lomex et al. 1989) and a 2-year NTP gavage study also in rats and mice (NTP 1985). An increased incidence of bronchioalveolar adenomas (benign lung tumors) was observed in mice after inhalation exposure for 2 years. No other neoplasms attributable to 1,3-dichloropropene were observed in this study. In contrast, both rats and mice developed neoplasms in the 2-year gavage study. An increased incidence of forestomach squamous cell papillomas and carcinomas was noted in both species. Male rats also developed an increased incidence of liver neoplastic nodules. Mice also developed transitional cell carcinoma of the urinary bladder and bronchioalveolar adenomas. The difference in carcinogenicity observed in the two studies may be related to the stabilizer present in the technical-grade 1,3-dichloropropene tested. The oral study used a compound containing epichlorohydrin as a stabilizer. Epichlorohydrin reportedly causes nasal and forestomach tumors in rats following chronic inhalation and oral exposure, respectively. The inhalation study tested a 1,3-dichloropropene compound containing a less toxic epoxidized soybean oil as a stabilizer. It may be of value to repeat the 2-year inhalation study with Telone II®b to evaluate the potential for carcinogenicity because the results in mice were equivocal. A carcinogenicity study by the oral route using a formulation without epichlorohydrin would help determine if the carcinogenicity observed in rats and mice treated with the formulation containing epichlorohydrin was due to 1,3-dichloropropene or the stabilizer.

An initiation-promotion study of cis-1,3-dichloropropene by dermal exposure in mice indicated that cis-1,3-dichloropropene was not an initiator of skin tumors (Van Duuren et al. 1979). Furthermore, cis-1,3-dichloropropene alone did not induce skin tumors after repeated dermal application for 74 weeks. No studies were located regarding the carcinogenic mechanism of action of 1,3-dichloropropene. Available data indicate, however, that 1,3-dichloropropene is mutagenic in prokaryotic and eukaryotic test systems and that it is a strong tissue irritant. Both properties may underlie the carcinogenic potential of 1,3-dichloropropene.

Genotoxicity. No data are available regarding the genotoxicity of 1,3-dichloropropene in humans after exposure by any route. In vivo animal studies are also lacking. 1,3-Dichloropropene is mutagenic in prokaryotic (Creedy et al. 1984; De Lorenzo et al. 1977; Eder et al. 1982a, 1982b; Haworth et al. 1983; Neudecker and Henschler 1986; Neudecker et al. 1977; Stolzenberg and Hine 1980; Talcott and King 1984; Vithayathil et al. 1983; Watson et al. 1987) and eukaryotic (Eder et al. 1987; Loveday et al. 1989; Sasaki et al. 1988; Schiffman et al. 1983; von der Hude et al. 1987) systems, which indicates that the chemical may be mutagenic in humans. The carcinogenicity of 1,3-dichloropropene also supports the possibility that it would be mutagenic; however, in vitro studies that compared the mutagenicity of purified 1,3-dichloropropene with that available commercially as technicalgrade 1,3-dichloropropene indicated that purified 1,3-dichloropropene is not mutagenic. In contrast, the impurities removed from the technical-grade 1,3-dichloropropene were highly mutagenic. Additional in vitro studies that focus on the mutagenicity of purified 1,3-dichloropropene versus the technical grade seem warranted at this time. Furthermore, considering the development of hematological malignancies in humans exposed to 1,3-dichloropropene, it may be valuable to conduct in vivo tests for chromosomal aberrations in humans or animals exposed to 1,3-dichloropropene.

Reproductive Toxicity. No information regarding the reproductive toxicity of 1,3-dichloropropene by any route of exposure in humans is available. Pharmacokinetic data in rats indicate that 1,3-dichloropropene or its metabolites are found in low concentrations in reproductive organs and tissues (Waechter and Kastl 1988). However, no effects on reproductive parameters of rats were found in a two-generation inhalation study (Breslin et al. 1989). Furthermore, no lesions attributable to 1,3-dichloropropene were observed after gross and histologic evaluation of reproductive tissues and organs in several animal studies. These studies include a two-generation reproductive/developmental inhalation study (Breslin et al. 1989), a lo-week inhalation reproductive study (Linnett et al. 1988), a 2-year inhalation study (Lomax et al. 1989), and a 2-year oral study (NTP 1985). No studies regarding reproductive effects in animals following dermal exposure were found; however, the results of the inhalation and oral studies indicate no reason to suspect that 1,3-dichloropropene would have reproductive effects by this route. Additional reproductive studies would not be useful at this time.

Developmental Toxicity. Both acute-duration (rats and rabbits) (Kloes et al. 1983) and intermediate-duration inhalation studies (rats) (Breslin et al. 1989) of developmental and reproductive effects have shown that 1,3-dichloropropene is not teratogenic. However, fetotoxicity in the rabbits could not be assessed because significant maternal toxicity at the highest concentration tested (300 ppm) resulted in the death of six of seven rabbits (Kloes et al. 1983). Maternal toxicity in rats, also at 300 ppm, may have resulted in fetotoxicity and the. subsequent decrease reported in fetuses per litter. Lower concentrations of 1,3-dichloropropene (150 ppm or less) were

not fetotoxic in these studies, although an exposure of 120 ppm to pregnant rats resulted in delayed ossification, which may have been due to decreased body weight of the dams. Human exposures to such high concentrations of 1,3-dichloropropene are not likely; therefore, further developmental toxicity studies would not be useful at this time.

Immunotoxicity. One clinical report regarding the development of a delayed-type hypersensitivity after skin contact in a 26-year-old worker occupationally exposed to 1,3-dichloropropene (Van Joost and de Jong 1988) indicates the possibility of immunotoxicity in humans. This report is supported by animal studies that document the development of delayed-type hypersensitivity in guinea pigs (Carreon and Wall 1983; Jeffrey 1987a; Jones 1988c; Mizell 1988b). The development of hematologic malignancies in three men occupationally exposed to 1,3-dichloropropene might also indicate immunotoxicity (Markovitz and Crosby 1984). Since the immune system may be a target of 1,3-dichloropropene toxicity, a battery of immune function tests may be warranted at this time. Even so, no animal studies showed adverse hematological effects, despite exposure by inhalation or gavage for intermediate or chronic duration (Lomax et al. 1989; NTP 1985; Stott et al. 1988; Til et al. 1973; Torkelson and Oyen et al. 1977). Furthermore, gross and histological examination of the lymph nodes and the thymus in several animal studies of inhalation and oral exposure revealed no lesions attributable to 1,3-dichloropropene (Lomax et al. 1989; NTP 1985; Parker et al. 1982; Stott et al. 1988).

Neurotoxicity. No neurotoxicity was observed in humans accidentally exposed to 1,3-dichloropropene at concentrations high enough to require medical attention (Markovitz and Crosby 1984). No studies regarding the neurotoxicity of 1,3-dichloropropene in animals were located. Gross and histological examination of brain, nerves, and the spinal cord from rats and mice after inhalation (Coate 1979a; Lomax et al. 1989; Stott et al. 1988) and oral exposure (NTP 1985) revealed no lesions attributable to 1,3-dichloropropene. Clinical signs that indicate possible neurotoxicity, however, were noted in rabbits after dermal exposure to high concentrations of 1,3-dichloropropene(Jones 1988b), and in rabbits after inhalation exposure to high concentrations of 1,3-dichloropropene (Kloes et al. 1983). These signs included ataxia, loss of the righting reflex, lacrimation, salivation, and lethargy. Further studies of more subtle neurological changes, such as nerve conduction velocity, may be warranted at this time.

Epidemiological and Human Dosimetry Studies. No studies were located regarding the epidemiology of 1,3-dichloropropene exposure. One pharmacokinetic study in humans, however, described a strong correlation between exposure levels during the application of 1,3-dichloropropene on farms and urinary excretion levels of 1,3-dichloropropene metabolites (Osterloh et al. 1984). In light of the possible human carcinogenicity of 1,3-dichloropropene, epidemiological studies of'carcinogenicity in, for

example, agricultural workers exposed occupationally, would be especially valuable. Additionally, long-term follow-up studies of chronic toxicity and carcinogenicity in people exposed to high concentrations of 1,3-dichloropropene at the site of a spill would be valuable. Chronic toxicity evaluation should focus on the lungs, liver, and kidneys, which are the primary target organs identified in animal studies. Epidemiological studies of chronic toxicity and carcinogenicity in populations residing near hazardous waste sites would also provide important information.

Biomarkers of Exposure and Effect. The only biomarker of exposure identified in the literature is the mercapturic acid metabolite of 1,3-dichloropropene found in the urine of animals exposed by inhalation (Fisher and Kilgore 1988b) and orally (Climie et al. 1979; Hutson et al. 1971) and humans exposed occupationally (Osterloh et al. 1974). In humans, a strong correlation was reported between occupational exposure levels and levels of the urinary metabolite. 1,3-Dichloropropene is rapidly cleared from the body; essentially no radioactivity was found in the carcasses of rats 48-96 hours after dosing with ^{14}C-labeled 1,3-dichloropropene (Hutson et al. 1971). Because 1,3-dichloropropene does not appear to accumulate in the body, only short-term and possibly intermediate-duration exposures could be assessed using the urinary metabolite as a biomarker. Although no pharmacokinetic studies have investigated chronic exposure, this duration of exposure might not be reliably assessed if some period of time has passed between the last exposure and biomarker analysis. Extensive hematological and clinical chemistry analyses have been performed in animal studies of intermediate and chronic exposure. No adverse effects were observed on either parameter; therefore, attempts to develop biomarkers that use easily obtained biological fluids may not be fruitful. Research to identify a biomarker would facilitate future medical surveillance, which can lead to early detection and treatment.

The effects identified in animal studies include respiratory tract hyperplasia, lung trauma, and an increased incidence of stomach, lung, and urinary bladder neoplasms. Effects noted in humans are nonspecific clinical signs. Thus, no easily evaluated, specific biomarkers used to characterize effects are available. Development of new biomarkers of effect requires a thorough knowledge of the health effects and more subtle physiological or biochemical changes caused by 1,3-dichloropropene.

Absorption, Distribution, Metabolism, and Excretion. 1,3-Dichloropro-Pene is absorbed by all routes of exposure. Absorption by the pulmonary (Stott and Kastle 1986) and gastrointestinal tracts (Climie et al. 1979; Hutson et al. 1971) is extensive, but quantitative information regarding dermal exposure was not located. Information regarding distribution was available only for the oral route. Following exposure of rats by gavage to radiolabeled 1,3-dichloropropene, radioactivity was widely distributed with the highest levels of radioactivity found in the nonglandular stomach and urinary bladder (Waechter and Kastl 1988). Steady-state blood levels of the

glutathione conjugate of 1,3-dichloropropene were observed within 15 minutes of inhalation exposure in rats, indicating that the chemical is rapidly absorbed and metabolized (Fisher and Kilgore 1989). The glutathione conjugate is then converted to the corresponding mercapturic acid, which is excreted in the urine, the primary route of excretion for both inhalation (Fisher and Kilgore 1989) and oral exposure (Climie et al. 1979; Huston et al. 1971). Significant quantities are also excreted as CO_2 in the expired air, with a much smaller portion excreted in the feces (Hutson et al. 1971). Available data are insufficient to reliably assess the relative rates of absorption, distribution, metabolism, and excretion. Even so, pharmacokinetic data indicate that absorption and excretion are rapid; only 4% of a ^{14}C-labeled dose was recovered from the carcasses of rats 48 hours after oral administration (Hutson et al. 1971). Absorption and excretion were not linear at high inhalation concentrations (300-900 ppm), indicating a saturable metabolic pathway (Stott and Kastl 1986). Comparison of the metabolism and excretion of 1,3-dichloropropene after single or repeated oral doses showed no differences (Waechter and Kastl 1988).

At this time, investigation of the absorption, distribution, metabolism, and excretion of 1,3-dichloropropene after exposure by all routes and duration categories would provide valuable information. Inhalation and dermal exposures are particularly important occupationally but are also important regarding humans residing near hazardous waste sites.

Comparative Toxicokinetics. In a study of humans occupationally exposed to 1,3-dichloropropene, the major urinary metabolite found was the mercapturic acid conjugate of 1,3-dichloropropene (Osterloh et al. 1984). A significant correlation was observed between exposure levels of 1,3-dichloropropene and excretion of the metabolite. Studies in rats (Climie et al. 1979; Fisher and Kilgore 1989; Hutson et al. 1971; Stott and Kastl 1986) and one study in mice (Dietz et al. 1982) support the identification of the mercapturic acid metabolite as the primary 1,3-dichloropropene metabolite. The excretion data in mice and rats are similar; excretion in urine is the primary route, followed by excretion of CO_2 in the expired air and then by excretion in the feces. It is reasonable to expect that excretion is similar in humans; therefore, rats would provide a good model for further pharmacokinetic and toxicity studies of 1,3-dichloropropene. Additional pharmacokinetic studies should focus on the rates of absorption, distribution, metabolism, and excretion, particularly by the dermal route, after acute, intermediate, and chronic exposures.

Mitigation of Effects. Information on the metabolism of 1,3-dichloropropene in humans (Osterloh et al. 1984) and animals (Dietz et al. 1982; Fisher and Kilgore 1988a) indicates that the major pathway occurs via conjugation with glutathione, which can occur in nasal tissue, the stomach, liver, and kidney. Since these organs and the urinary bladder are target organs of the toxicity of 1,3-dichloropropene, it is not clear whether this

conjugation represents a detoxifying or a toxifying mechanism. Studies that determine whether the parent 1,3-dichloropropene compound or the conjugated product(s) represent the putative toxicant would be useful in planning research aimed to develop agents that could increase the conjugation (if a detoxifying mechanism) or that would deplete glutathione (if a toxifying mechanism), thereby mitigating the effects.

2.9.3 On-going Studies

No information regarding current studies of the health effects of 1,3-dichloropropene was located.